Index Issue

# SCIENCE

26 June 1959

Volume 129, Number 336



AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

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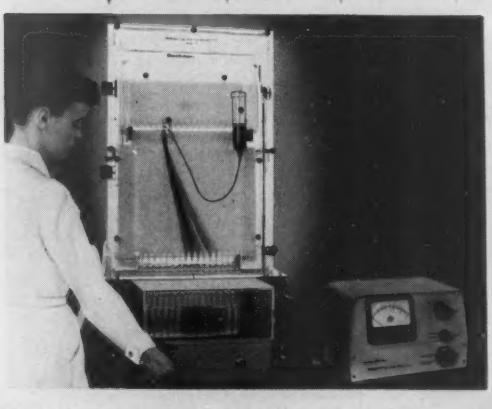
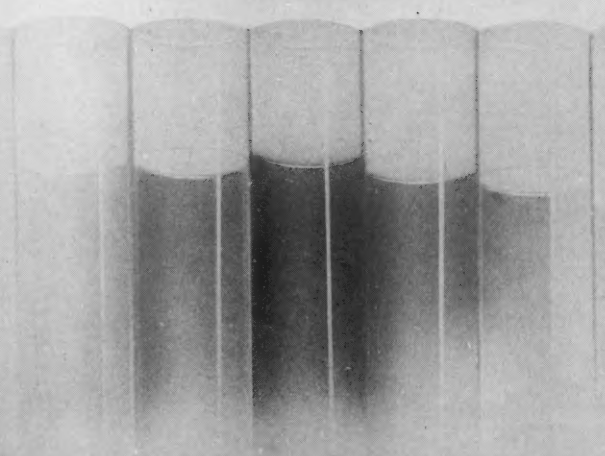
**TO TOUGH SEPARATION**

**PROBLEMS**





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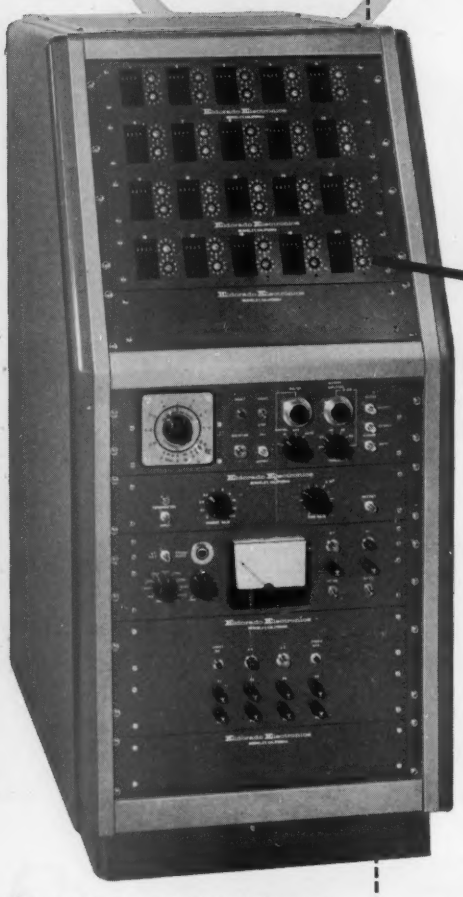


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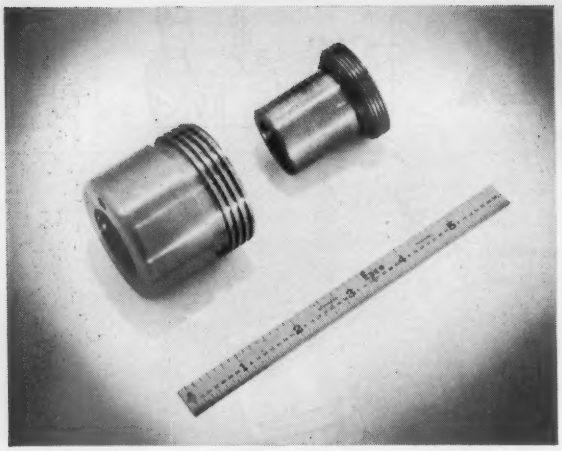

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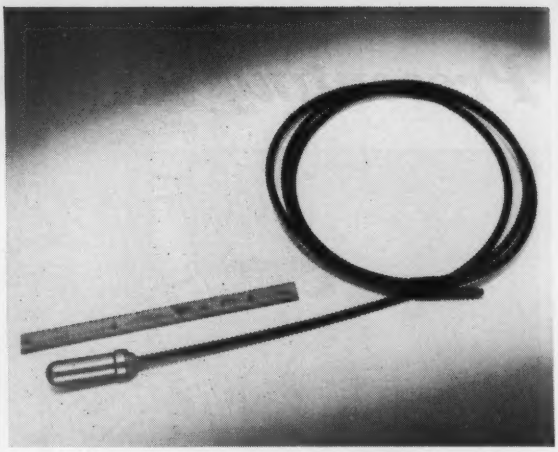

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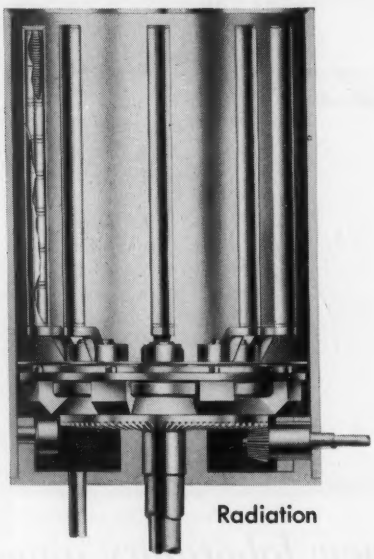

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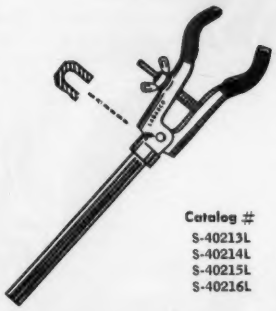

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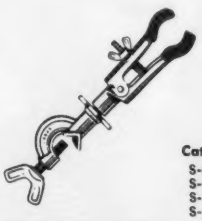

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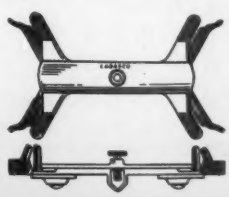

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26 June 1959, Volume 129, Number 3365

# SCIENCE



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## Bigness Has Its Place

With government appropriations for scientific and technological projects growing ever larger, some scientists are coming to wonder whether success will spoil basic research. Instead of seeking answers to questions that puzzle them, so the argument runs, scientists are caught up in projects that have little to do with basic research, however important these projects may be from the viewpoint of our military security or of our efforts to promote international good will. Moreover, the argument continues, the projects are designed on such a grand scale that many scientists spend their time in administrative activities rather than in creative thought. We agree that there is something to this line of thought, but if prosperity has some pitfalls it also has a few advantages.

Work on some of the most fundamental and interesting scientific questions seems now to have reached a stage where further progress requires the construction of extraordinarily expensive and complicated equipment. In the study of the structure of matter, for example, many physicists are puzzled by the apparently large number of elementary particles. The feeling is that elementary particles, if really elementary, must be few in number. Consequently, physicists suspect that a closer look at their structure will reveal an underlying, unifying pattern, much as resulted from a closer look at the structure of the chemical elements. But a detailed probing of the elementary particles of physics requires nuclear accelerators even more powerful, and hence more expensive to build and more complicated to run, than those now in operation.

Another example of the possibility of a program of great size leading to a fundamental advance in science may be taken from the broad field of space exploration. Recovery of materials from Mars or Venus, or the study of such materials by remote sampling techniques, may produce results bearing on such basic questions as the origin of life. Everyone knows, of course, that life does not now arise spontaneously on the earth, but the theory of biochemical evolution holds that life develops spontaneously when the conditions are right and that once upon a time on the earth conditions *were* right. Proof that life exists on another planet, and the study of its forms, could fill important gaps in this theory.

Our defense of bigness, then, is that in some areas of research it may be a necessary condition for further advance. We hardly wish to claim, however, that bigness is also a sufficient condition for that advance. The value of the arguments of those people who have doubts about bigness lies in their refutation of this latter claim—which, of course, is never stated so baldly. One measure sometimes proposed as an aid to basic research is that the government should not finance projects but support people. It should give blank checks to the best scientists to work on problems that interest them. But one can favor support for some individuals and still see value in the support of projects employing large groups of specialists operating as teams.

It certainly is no secret that the reason why the government is playing such a large role in the support of science is that science is playing such a large role in the prestige and power of nations. New appropriations for research do not spring from sudden increases in the love of learning. But perhaps in the not-too-distant future, scientists will say of some of our present huge projects that the resulting gains in our understanding of nature fully warranted the effort, even though hope of such gains was not the only reason why the projects received support.—J.T.

26 June 1959, Volume 129, Number 3365 SCIENCE

# A Case History in Biological Research

Chance and the exchange of ideas played roles in the discovery that genes control biochemical events.

Edward L. Tatum

In casting around for a new approach, I considered that much of biochemical genetics has been and will be covered by George Beadle and Joshua Lederberg, and in many symposia and reviews in which many aspects have been and will be considered in greater detail and with greater competence than I can hope to present them here. It occurred to me that perhaps it might be instructive, valuable, and interesting to use an approach which I have attempted to define by the title "A case history in biological research."

In the development of this case history I hope to point out some of the factors involved in all research—specifically, the dependence of scientific progress on knowledge and concepts provided by investigators, past and present, all over the world; on the free interchange of ideas within the international scientific community; on the hybrid vigor resulting from cross-fertilization between disciplines; and last but not least, on chance, geographical proximity, and opportunity. I would like, finally, to complete this case history with a brief discussion of the present status of the field and a prognosis of possible developments.

Under the circumstances, I hope I will be forgiven if this presentation is given from a personal viewpoint. After graduating from the University of Wisconsin in chemistry, I was fortunate in having the opportunity to do graduate work in biochemistry and microbiology at that university under the direction and leadership of W. H. Peterson and E. B. Fred. At that time, in the early 1930's, one of the exciting areas being opened concerned the so-called "growth factors" for microorganisms, for the most part as yet mysterious and unidentified. I became deeply involved in this field and was fortunate to be able, in collaboration with H. G. Wood, then visiting at Wisconsin, to identify one of the required growth factors for propionic acid bacteria as the recently synthesized vitamin $B_1$ or thiamine (*1*). This was before the universality of the need for the B vitamins, and the enzymatic basis of this requirement, had been clearly defined. Lwoff and Knight had already envisaged a correlation of the need of microorganisms for "growth factors" with failure of synthesis and had correlated this failure with evolution, particularly in relation to the complex environment of "fastidious" pathogenic microorganisms. However, the tendency at this time was to consider "growth factors" to be highly individual requirements, peculiar to particular strains or species of microorganisms isolated from nature, and variation of microorganisms in these respects was not generally considered to be related to gene mutation and variation in higher organisms. Actually, my ignorance of and naïveté about genetics was probably typical of most biochemists and microbiologists of the time, my only contact with genetic concepts having been a course primarily on vertebrate evolution.

After completing graduate work at Wisconsin I was fortunate in being able to spend a year studying at the University of Utrecht with F. Kögl, the discoverer of the growth factor biotin, and to work in the same laboratory with Nils Fries, who already had made significant contributions in the field of nutrition and growth of fungi.

At this time Beadle was just moving to Stanford University and invited me, as a biochemist, to join him in the further study of the eye-color hormones of *Drosophila*, which he and Ephrussi in their work at the California Institute of Technology and in Paris had so brilliantly established as diffusible products of gene-controlled reactions. During this, my first contact with modern genetic concepts, as a consequence of a number of factors—the observation of Khouvine, Ephrussi, and Chevais (*2*) in Paris that dietary tryptophan was concerned with the production of eye-color hormone in *Drosophila*, our studies on the nutrition of *Drosophila* in aseptic culture (*3*), and the chance contamination of one of our cultures of *Drosophila* with a particular bacterium—we were able to isolate the $v^+$ hormone in crystalline state from a bacterial culture supplied with tryptophan (*4*) and, with A. J. Haagen-Smit, to identify it as kynurenine (*5*), originally isolated by Kotake and later structurally identified correctly by Butenandt. It has since been recognized that kynurenine occupies a central position in tryptophan metabolism in many organisms other than insects, including mammals and fungi.

Dr. Tatum is a member of the staff of the Rockefeller Institute. This article is the lecture which he delivered in Stockholm, Sweden, on 11 December 1958, when he received the Nobel prize in medicine and physiology, a prize which he shared with George W. Beadle and Joshua Lederberg. It is published by permission of the Nobel Foundation. Dr. Beadle's lecture appears on page 1715 of this issue. Dr. Lederberg's lecture will be published in a subsequent issue.

## Work with Neurospora

At about this time, as the result of many discussions and considerations of the general biological applicability of chemical genetic concepts, and stimulated by the wealth of potentialities among the microorganisms and by their variation in nature with respect to nutritional requirements, we began our work with the mold *Neurospora crassa*.

I shall not enumerate the factors involved in our selection of this organism for the production of chemical or nutritionally deficient mutants but must take this opportunity to reiterate our indebtedness to the previous basic findings of a number of investigators. Foremost among these was B. O. Dodge, who established this ascomycete as a most suitable organism for genetic studies (*6*); and C. C. Lindegren (*7*), who became interested in *Neurospora* through T. H. Morgan, a close friend of Dodge.

Our use of *Neurospora* for chemical genetic studies would also have been much more difficult, if not impossible, without synthetic biotin, available as a result of the work of Kögl (*8*) and du Vigneaud (*9*). In addition, the investigations of Nils Fries on the nutrition of *Ascomycetes* (*10*) were most helpful, as is shown by the fact that the synthetic minimal medium used with *Neurospora* for many years was that described by him, supplemented only with biotin; it has ordinarily been referred to since then as "Fries medium." It should also be pointed out that the experimental feasibility of producing the desired nutritionally deficient mutant strains depended on the early pioneering work of Roentgen, with x-rays, and on that of H. J. Muller, on the mutagenic effect of x-rays and ultraviolet light on *Drosophila*. All that was needed was to put these various facts and findings together to produce in the laboratory, with irradiation, nutritionally deficient (auxotrophic) mutant strains of *Neurospora* and to show that each single deficiency produced was associated with the mutation of a single gene (*11*).

Having thus successfully tested with *Neurospora* the basic premise that the biochemical processes concerned with the synthesis of essential cell constituents are gene-controlled, and alterable as a consequence of gene mutation, we felt that it would be a desirable and natural step to carry this approach to the bacteria, in which so many and such varied naturally occurring growth-factor requirements were known, to see whether analogous nutritional deficiencies followed exposure of the bacteria to radiation. As is known to all of you, the first mutants of this type were successfully produced in *Acetobacter* and in *Escherichia coli* (*12*), and the first step had been taken in bringing the bacteria into the fold of organisms suitable for genetic study.

## Coincidence and Chance

Now, to point out some of the curious coincidences or twists of fate involved in science: One of the first series of mutants in *Neurospora* which was studied intensively from the biochemical viewpoint was that concerned with the biosynthesis of tryptophan. In connection with the role of indole as a precursor of tryptophan, we wanted also to study the reverse process, the breakdown of tryptophan to indole, a reaction typical of the bacterium *E. coli*. For this purpose we obtained, from the bacteriology department at Stanford, a typical *E. coli* culture, designated K-12. Naturally, this strain was later used for the mutation experiments just described, and a variety of biochemically marked mutant strains of *E. coli* K-12 were soon available. Esther Zimmer, who later became Esther Lederberg, assisted in the production and isolation of these mutant strains.

Another interesting coincidence is that F. J. Ryan spent some time on leave from Columbia University at Stanford, working with *Neurospora*. Shortly after I moved to Yale University in 1945, Ryan encouraged Lederberg, then a medical student at Columbia who had worked with Ryan on *Neurospora*, to spend some time with me at Yale University. As all of you know, Lederberg was successful in showing genetic recombination between mutant strains of *E. coli* K-12 (*13*) and never returned to medical school but continued his brilliant work on bacterial recombination at Wisconsin. In any case, the first demonstration of a process analogous to a sexual process in bacteria was successful only because of the clear-cut nature of the genetic markers available, which permitted detection of this very rare event, and because of the combination of circumstances which had provided those selective markers in one of the rare strains of *E. coli* capable of recombination. In summing up this portion of this case history, then, I wish to emphasize again the role that coincidence and chance played in the sequence of developments, but yet more strongly to acknowledge the even greater contributions of my close friends and associates, Beadle and Lederberg, with whom it is a rare privilege and honor to share this award.

## Basic Concepts

Now for a brief and necessarily somewhat superficial mention of some of the problems and areas of biology to which these relatively simple experiments with *Neurospora* have led and contributed. First, however, let us review the basic concepts involved in this work. Essentially these are (i) that all biochemical processes in all organisms are under genic control; (ii) that these over-all biochemical processes are resolvable into a series of individual stepwise reactions; (iii) that each single reaction is controlled in a primary fashion by a single gene—or, in other terms, in every case a 1:1 correspondence of gene and biochemical reaction exists, such that (iv) mutation of a single gene results only in an alteration in the ability of the cell to carry out a single primary chemical reaction. As has repeatedly been stated, the underlying hypothesis, which in a number of cases has been supported by direct experimental evidence, is that each gene controls the production, function, and specificity of a particular enzyme.

Important experimental implications of these relations are that each and every biochemical reaction in a cell of any organism, from a bacterium to man, is theoretically alterable by gene mutation, and that each such mutant cell strain differs in only one primary way from the nonmutant parental strain. It is probably unnecessary to point out that these experimental expectations have been amply supported by the production and isolation, by many investigators during the last 15 or more years, of biochemical mutant strains of microorganisms in almost every species tried—bacteria, yeasts, algae, and fungi.

## Biochemical Mutants

It is certainly unnecessary for me to do more than point out that mutant strains such as those produced and isolated first in *Neurospora* and *Escherichia coli* have been of primary utility as genetic markers in detecting and eluci-

dating the details of the often exotic mechanisms of genetic recombination of microorganisms.

Similarly, it seems superfluous even to mention the proven usefulness of mutant strains of microorganisms in unraveling the detailed steps involved in the biosynthesis of vital cellular constituents. I would like to list, however, a few of the biosynthetic sequences and biochemical interrelationships which owe their discovery and elucidation largely to the use of biochemical mutants. These include the synthesis of the aromatic amino acids via dehydroshikimic and shikimic acids (*14*), by way of prephenic acid to phenylalanine (*15*), and by way of anthranilic acid, indole glycerol phosphate (*16*), and condensation of indole with serine to give tryptophan (*17*); the conversion of tryptophan via kynurenine and 3-hydroxyanthranilic acid to niacin (*18*); the biosynthesis of histidine (*19*); the biosynthesis of isoleucine and valine via the analogous dihydroxy and keto acids (*20*); the biosynthesis of proline and ornithine from glutamic acid (*21*); and the synthesis of pyrimidines via orotic acid (*22*).

If the postulated relationship of gene to enzyme is correct, several consequences can be predicted. First, mutation should result in the production of a changed protein, which might be enzymatically inactive, might have intermediate activity, or might have otherwise detectably altered physical properties. The production of such proteins, changed, in respect to heat stability, enzymatic activity, or other properties such as activation energy, by mutant strains, has indeed been demonstrated in a number of instances (*23*). Recognition of the molecular bases of these changes must await detailed comparison of their structures with those of the normal enzyme, by means of techniques similar to the elegant methods of Sanger. That the primary effect of gene mutation may be as simple as the substitution of a single amino acid by another and may lead to profound secondary changes in protein structure and properties has recently been strongly indicated by the work of Ingram on hemoglobin (*24*). It seems inevitable that induced mutant strains of microorganisms will play a most important part in providing material for the further examination of these problems.

A second consequence of the postulated relationship stems from the concept that the genetic constitution defines the potentialities of the cell, the time and degree of expression of these potentialities being to a certain extent modifiable by the cellular environment. The analysis of this type of secondary control at the biochemical level is one of the important and exciting new areas of biochemistry. This deals with the regulation and integration of biochemical reactions by means of feedback mechanisms restricting the synthesis or activities of enzymes (*25*) and, through substrate induced biosynthesis of enzymes (*26*). It seems probable that some gene mutations may affect biochemical activities at this level (modifiers and suppressors) and that chemical mutants will prove of great value in the analysis of the details of such control mechanisms.

An equally fascinating newer area of genetics, opened by Benzer (*27*) with bacteriophage, is that of the detailed correlation of fine structure of the gene in terms of mutation and recombination with fine structure in terms of activity. Biochemical mutants of microorganisms have recently opened this area to investigation at two levels of organization of genetic material. The higher level relates to the genetic linkage of nonallelic genes concerned with sequential biosynthetic reactions. This has been shown by Demerec and by Hartman in the biosynthesis of tryptophan and histidine by *Salmonella* (*28*).

At a finer level of organization of genetic material, the biological versatility of *Neurospora* in forming heterocaryotic cells has permitted the demonstration (*29*) that genes damaged by mutation in different areas, within the same locus and controlling the same enzyme, complement each other in a heterocaryon in such a way that synthesis of enzymatically active protein is restored, perhaps in a manner analogous to the reconstitution of ribonuclease from its *a* and *b* constituents, by the production in the cytoplasm of an active protein from two gene products defective in different areas. This phenomenon of complementation, which appears also to take place in *Aspergillus* (*30*), permits the mapping of genetic fine structure in terms of function and should lead to further information on the mechanism of enzyme production and clarification of the role of the gene in enzyme synthesis.

The concepts of biochemical genetics have already been, and will undoubtedly continue to be, significant in broader areas of biology. Let me cite a few examples from microbiology and medicine.

## Microbial Genetics and Antibiotics

In microbiology the roles of mutation and selection in evolution are coming to be better understood through the use of bacterial cultures of mutant strains. In more immediately practical ways, mutation has proven of primary importance in the improvement of yields of important antibiotics; the classic example is penicillin, the yield of which has gone up from around 40 units per milliliter of culture shortly after its discovery by Fleming to somewhat over 4000 units as the result of a long series of experimentally produced mutational steps. On the other side of the coin, the mutational origin of antibiotic-resistant microorganisms is of definite medical significance. The therapeutic use of massive doses of antibiotics to reduce the numbers of bacteria which by mutation could develop resistance is a direct consequence of the application of genetic concepts. So is the increasing use for therapeutic purposes of two antibiotics in combination; resistance to both of them would require the simultaneous mutation of two independent characters.

## Microbial Genetics and Mammalian Cells

As an important example of the application of these same concepts of microbial genetics to mammalian cells, we may cite the probable mutational origin of resistance to chemotherapeutic agents in leukemic cells (*31*) and the increasing and effective use of two or more chemotherapeutic agents simultaneously in the treatment of this disease. In this connection it should be pointed out that the most effective chemotherapeutic agents in cancer so far found are those which interfere with deoxyribonucleic acid synthesis, and that more detailed information on the biochemical steps involved in this synthesis is making possible a more rational design of such agents. Parenthetically, I want to emphasize the analogy between the situation in a bacterial culture consisting of two or more cell types and that involved in the survival of a malignant cell, regardless of its origin, in a population of normal cells. Changes in the cellular environment such as are involved in chemotherapy would be expected to affect the metabolic efficiency of an altered cell, and hence to affect its growth characteristics. However, as in the operation of selection pressures in bacterial popu-

lations, based on the interaction between cell types, it would seem that the effects of chemotherapeutic agents on the efficiency of selection pressures among mammalian cell populations can be examined most effectively only in controlled mixed populations of the cell types concerned.

In other areas in cancer, the concepts of genetics are becoming increasingly important, both theoretically and practically. It seems probable that neoplastic changes are directly correlated with changes in the biochemistry of the cell. The relationships between deoxyribonucleic acid, ribonucleic acid, and enzymes which have been recognized during the last few decades lead one to look for the basic neoplastic change in one of these intimately interrelated hierarchies of cellular materials.

In relation to deoxyribonucleic acid, hereditary changes are now known to take place as a consequence of mutation, or of the introduction of new genetic material through virus infection (as in transduction) or directly (as in transformation). Although each of these related hereditary changes may theoretically be involved in cancer, definite evidence is available only for the role of viruses, stemming from the classic investigations of Rous on fowl sarcoma (*32*). At the ribonucleic acid level of genetic determination, any one of these classes of change might take place, as in the ribonucleic acid containing viruses, and result in a heritable change, perhaps of the cytoplasmic type, semiautonomous with respect to the gene. At the protein level, regulatory mechanisms determining gene activity and enzyme synthesis, as mentioned earlier, likewise provide promising areas for exploration.

Among the many exciting applications of microbial-genetic concepts and techniques to the problems of cancer, may I mention in addition the exploration by Klein (*33*) of the genetic basis of the immunological changes which distinguish the cancer cell from the normal cell and the studies of Puck (*34*) and of Eagle (*35*) on the culture, nutrition, morphology, and mutation of isolated normal and malignant mammalian cells. Such studies are basic to our exploration and to our eventual understanding of the origin and nature of the change to malignancy.

No matter what the origin of a cancer cell, however, and what the precise genetic level at which the primary change takes place, it is not too much to hope and expect eventually to be able to correct or alleviate the consequences of the metabolic defect, just as a closer understanding of a heritable metabolic defect in man makes possible the correction or alleviation of the defect. In terms of biochemical genetics, the consequences of a metabolic block may be rectified by dietary limitation of the precursor of an injurious accumulation product (aromatic amino acids in phenylketonuria) or by supply of the essential end product from without the cell, the specific blood protein in hemophilia, or a specific essential nutrient molecule such as a vitamin.

## Predictions

I do not have space for more examples. Perhaps, however, I will be pardoned if I venture briefly to make a few more predictions and express some hopes for the future.

It does not seem unrealistic to expect that, as more is learned about control of cell machinery and heredity, we will see the complete conquest of many of man's ills, including hereditary defects in metabolism and the currently more obscure conditions such as cancer and the degenerative diseases, just as diseases of bacterial and viral etiology are now being conquered.

With a more complete understanding of the functioning and regulation of gene activity in development and differentiation, these processes may be more efficiently controlled and regulated, not only to exclude structural or metabolic errors in the developing organism but also to produce better organisms.

Perhaps within the lifetime of some of us, the code of life processes tied up in the molecular structure of proteins and nucleic acids will be broken. This may permit the improvement of all living organisms by processes which we might call biological engineering.

This might proceed in stages, from in vitro biosynthesis of better and more efficient enzymes to biosynthesis of the corresponding nucleic acid molecules, and to introduction of these molecules into the genome of organisms, either through injection, through introduction of viruses into germ cells, or through a process analogous to transformation. Alternatively, it may be possible to reach the same goal by a process involving directed mutation.

As a biologist, and more particularly as a geneticist, I have great faith in the versatility of the gene and of living organisms in providing the material with which to meet the challenges of life at any level. Selection, survival, and evolution take place in response to environmental pressures of all kinds, including sociological and intellectual. In the larger view, the dangerous and often poorly understood and poorly controlled forces of modern civilization, including atomic energy and its attendant hazards, are but more complex and more sophisticated environmental challenges of life. If man cannot meet those challenges, in a biological sense he is not fit to survive.

However, it may confidently be hoped that, with real understanding of the roles of heredity and environment and with the resulting improvement in man's physical capacities and greater freedom from physical disease, will come an improvement in his approach to, and understanding of, sociological and economic problems. As in any area of scientific research, a problem clearly seen is already half solved. Hence, a renaissance may be foreseen, in which the major sociological problems will be solved and mankind will take a big stride towards the state of world brotherhood and mutual trust and well-being envisaged by Alfred Nobel.

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# Genes and Chemical Reactions in Neurospora

The concepts of biochemical genetics began with Garrod's "inborn errors" and have evolved gradually.

George W. Beadle

On this occasion of sharing the high honor of a Nobel award with Edward L. Tatum for our "discovery that genes act by regulating chemical events," and with Joshua Lederberg for his related "discoveries concerning the organization of the genetic material of bacteria," it seems appropriate that I sketch briefly the background events that led to the work on *Neurospora* that Tatum and I initiated in 1940. I shall leave to my corecipients of the award the task of describing in detail the developments in *Neurospora* that followed our first success, and the relation of this to the rise of bacterial genetics, which has depended largely on studies of genetic recombination following conjugation and transduction.

I shall make no attempt to review the entire history of biochemical genetics, for this has been done elsewhere (*1–4*).

## Anthocyanins and Alcaptonuria

Soon after de Vries, Correns, and Tschermak "rediscovered" Mendel's 1865 paper and recognized its full significance, investigators in the exciting new field, which was to be called genetics, naturally speculated about the physical nature of the "elements" of Mendel and the manner of their action. Renamed genes, these units of inheritance were soon found to be carried in the chromosomes.

One line of investigation that was destined to reveal much about what genes do was started by Wheldale (later name Onslow, by marriage) in 1903. It began with a genetic study of flower pigmentation in snapdragons. But soon the genetic observations began to be correlated with the chemistry of the anthocyanin and related pigments that were responsible. The material was favorable for both genetic and chemical studies, and the work has continued to yield new information ever since and almost without interruption. Many workers and many species of plants have been involved (*1–5*).

It became clear very soon that a number of genes were involved and that they acted by somehow controlling the onset of various identifiable and specific chemical reactions. Since an understanding of the genetics helped in interpreting the chemistry and vice versa, the anthrocyanin work was well known to both geneticists and biochemists. It significantly influenced the thinking of both fields and thus had great importance in further developments.

A second important line of investigation was begun even earlier by the Oxford physician-biochemist Sir Archibald E. Garrod. At the turn of the century he was interested in a group of congenital metabolic diseases in man, which he later named "inborn errors of metabolism." There are now many diseases so described; in fact, this has come to be recognized as a category of diseases of major medical importance.

One of the first "inborn errors" to be studied by Garrod was alcaptonuria. Its most striking symptom is blackening of urine on exposure to air. It had been recorded medically long before Garrod became interested in it, and important aspects of its biochemistry were understood. The substance responsible for blackening of the urine is alcapton or homogentisic acid (2,5-dihydroxyphenylacetic acid). Garrod suggested early that alcaptonuria behaved in inheritance as though it were differentiated by a single recessive gene.

By 1908 a considerable body of knowledge about alcaptonuria had accumulated. This was brought together and interpreted by Garrod in his Croonian lectures and in the two editions of his book, *Inborn Errors of Metabolism,* which were based on them (*6*). It was his belief that alcaptonuria was the result of inability on the part of affected individuals to cleave the ring of homogentisic acid as do normal individuals. He believed this to be due to absence or inactivity of the enzyme that normally catalyzes this reaction. This in turn was dependent on the absence of the normal form of a specific gene.

Thus, Garrod had clearly in mind the concept of a gene-enzyme-chemical-reaction system in which all three entities were interrelated in a very specific way. In the 1923 edition of *Inborn Errors* (*6*) he wrote: "We may further conceive that the splitting of the benzene ring of homogentisic acid in normal metabolism is the work of a special enzyme, that in congenital alcaptonuria this enzyme is wanting. . . ."

Failure to metabolize an intermediate

The author is chairman of the Division of Biology at California Institute of Technology, Pasadena. At present he is Eastman visiting professor at Oxford University, Oxford, England. This article is the lecture which he delivered in Stockholm, Sweden, 11 December 1958, on receiving the Nobel prize in medicine and physiology. It is published with the permission of the Nobel Foundation.

compound when its normal pathway is thus blocked by a gene-enzyme defect was a part of the interpretation and accounted for the accumulation and excretion of homogentisic acid. Garrod recognized this as a means of identifying an intermediate compound that might otherwise not appear in sufficient amounts to be detected.

He also clearly realized that alcaptonurics would be used experimentally to explore the metabolic pathways by which homogentisic acid was formed. He summarized a large body of evidence indicating that when normal precursors of homogentisic acid are fed to alcaptonurics there is an almost quantitative increase in homogentisic acid excretion. In this way evidence was accumulated that phenylalanine, tyrosine, and the keto acid analog of the latter were almost certainly the direct precursors of homogentisic acid.

Despite the simplicity and elegance of Garrod's interpretation of alcaptonuria and other inborn errors of metabolism as gene defects which resulted in inactivity of specific enzymes and thus in blocked reactions, his work had relatively little influence on the thinking of the geneticists of his time. Bateson's *Mendel's Principles of Heredity* and a few other books of its time discuss the concept briefly. But up to the 1940's, no widely used later textbook of genetics that I have examined even so much as refers to alcaptonuria. It is true that a number of other workers had seriously considered that genes might act in regulating chemical reactions by way of enzymes (*1–5*). But there was no other known instance as simple as alcaptonuria. It is interesting—and significant, I think—to note that it was approximately 50 years after Garrod proposed his hypothesis before it was anything like fully verified through the resolution into six enzymatically catalyzed steps of phenylalanine-tyrosine metabolism via the homogentisic acid pathway, and by the clear demonstration that homogentisate oxidase is indeed lacking in the liver of an alcaptonuric (*7*). Perhaps it is also well to recall that it was not until 1926 that the first enzyme was isolated in crystalline form and shown in a convincing way to consist solely of protein.

## Eye Pigments of Drosophila

I shall now shift to a consideration of an independent line of investigation which ended up with conclusions very much like those of Garrod and which led directly to the work with *Neurospora* that Tatum and I subsequently began.

In 1933, Boris Ephrussi came to the California Institute of Technology to work on developmental aspects of genetics. During his stay he and I had many long discussions in which we deplored the lack of information about the manner in which genes act on development. This we ascribed to the fact that the classical organisms of experimental embryology did not lend themselves readily to genetic investigation. Contrariwise, those plants and animals about which most was known genetically had been little used in studies of development.

It would be worth while, we believed, to attempt to remedy this situation by finding new ways experimentally to study *Drosophila melanogaster*—which, genetically, was the best understood organism of the time. Tissue-culture techniques seemed to offer hope. In the spring of 1935 we joined forces in Ephrussi's section of l'Institut de Biologie Physio-chimique in Paris, resolved to find ways of culturing tissues of the larvae of *Drosophila*.

After some discouraging preliminary attempts, we followed Ephrussi's suggestion and shifted to a transplantation technique. It was our hope that in this way we could make use of nonautonomous genetic characters as a means of investigating gene action in development.

*Drosophila* larvae are small, and we were told by a noted Sorbonne authority on the development of Diptera that the prospects were not good. In fact, he said, they were terrible.

But we were determined to try, so we returned to the laboratory, made micropipettes, dissected larvae, and attempted to transfer embryonic buds from one larva to the body cavity of another. The results were discouraging. But we persisted and finally one day discovered that we had produced a fly with three eyes. Although our joy was great over this small success, we immediately began to worry about three points: First, could we do it again? Second, if we could, would we be able to characterize the diffusible substances responsible for interactions between tissues of different genetic types? And, third, how many nonautonomous characters could we find?

We first investigated the sex-linked eye-color mutant vermilion because of the earlier finding of Sturtevant that in gynandromorphs genetically vermilion eye tissue often fails to follow the general rule of autonomy (*8*).

Gynandromorphs may result if, in an embryo that begins development as a female from an egg with two X chromosomes, one X chromosome is lost during an early cleavage, giving rise to a sector that has one X chromosome and is male. If the original egg is heterozygous for a sex-linked gene—say vermilion—and the lost chromosome carries the normal allele, the male sector will be genetically vermilion, whereas the female parts are normal or wild type. (Other sex-linked characters like yellow body or forked bristles can be used as independent markers to reveal genetic constitution in most parts of the body.)

Yet in Sturtevant's gynandromorphs, in which only a small part of the body, including eye tissue, was vermilion, the appearance of that tissue was usually not vermilion but wild type—as though some substance had diffused from wild-type tissue to the eye and caused it to become normally pigmented.

It was on the basis of this observation that Ephrussi and I transplanted vermilion eyes into wild-type larvae. The result was as expected—the transplanted eyes were indeed wild type.

At that time there were some 26 separate eye-color genes known in *Drosophila*. We obtained stocks of all of them and made a series of transplants of mutant eyes into wild-type hosts. We found only one other clear-cut nonautonomous eye character. This was cinnabar, a bright red eye color like vermilion but differentiated by a second chromosome recessive gene. We had a third less clear case, claret, but this was never entirely satisfactory from an experimental point of view because it was difficult to distinguish claret from wild-type eyes in transplants.

The vermilion and cinnabar characters are alike in appearance; both lack the brown pigment of the wild-type fly but retain the bright red component. Were the diffusible substances that caused them to develop brown pigment when grown in wild-type hosts the same or different? If the same, reciprocal transplants between the two mutants should give mutant transplanted eyes in both cases. If two separate and independent substances were involved, such reciprocal transplants should give wild-type transplanted eyes in both instances.

We made the experiment and were much puzzled that neither of these results was obtained. A cinnabar eye in a vermilion host remained cinnabar, but a vermilion eye in a cinnabar host became wild-type.

To explain this result we formulated the hypothesis that there must be two diffusible substances involved, one formed from the other, according to the scheme:

precursor → $v^+$ substance → $cn^+$ substance → pigment . . .,

where $v^+$ substance is a diffusible material capable of making a vermilion eye become wild type and $cn^+$ substance is capable of doing the same to a cinnabar eye (*9*).

The vermilion (*v*) mutant gene blocks the first reaction, and the cinnabar (*cn*) mutant gene interrupts the second. A vermilion eye in a cinnabar host makes pigment because it can, in its own tissues, convert the $v^+$ substance into $cn^+$ substance and pigment. In it, the second reaction is not blocked.

This scheme involves the following concepts: (i) a sequence of two gene-regulated chemical reactions, one gene identified with each; (ii) the accumulation of intermediates prior to blocked reactions; (iii) the ability of the mutant blocked in the first reaction to make use of an intermediate accumulated as a result of a genetic interruption of the second reaction. The principle involved is the same as that employed in the cross-feeding technique later so widely used in detecting biosynthetic intermediates in microorganisms.

What was later called the one-gene–one-enzyme concept was clearly in our minds at this time, although, as I remember, we did not so designate it.

Ours was a scheme closely similar to that proposed by Garrod for alcaptonuria, except that he did not have genes that blocked an adjacent reaction in the sequence. But at the time we were unaware of Garrod's work, partly because geneticists were not in the habit of referring to it and partly because we had failed to explore the literature. Garrod's book was available in many libraries.

We continued the eye-color investigations at the California Institute of Technology, Ephrussi having returned there to spend part of 1936. Late in the year, Ephrussi returned to Paris and I went for a year to Harvard; we continued to work along similar lines. We identified the source of diffusible substances—fat bodies and malpighian tubercules—and began to devise ways of determining their chemical nature. In this I collaborated to some extent with Kenneth Thimann.

In the fall of 1937 I moved to Stanford, where Tatum shortly joined me, to take charge of the chemical aspects of identifying the eye-color substances. Yvonne Khouvine worked in a similar capacity with Ephrussi. We made progress slowly. Ephrussi and Khouvine discovered that under certain conditions feeding tryptophan had an effect on vermilion eye color. Following this lead, Tatum found—through accidental contamination of an aseptic culture containing tryptophan and test flies—an aerobic *Bacillus* that converted tryptophan into a substance highly active in inducing formation of brown pigment in vermilion flies. He soon isolated and crystallized this, but its final identification was slowed down by what later proved to be a sucrose molecule esterified with the active compound.

A. Butenandt and his co-workers (*10*) in Germany, who had been collaborating with Kühn on an analogous eye-color mutant in the meal moth *Ephestia,* and Amano *et al.* (*11*), working at Osaka University, showed that $v^+$ substance was kynurenine. Later, Butenandt and Hallmann (*12*) and Butenandt *et al.* (*13*) showed that our original $cn^+$ substance was 3-hydroxykynurenine.

Thus was established a reaction series of the kind we had originally conceived. When the known chemicals are substituted, it is as follows:

Tryptophan
↓
N-Formylkynurenine
↓
Kynurenine
↓
3-Hydroxykynurenine
↓
Brown pigment

## A New Approach

Isolating the eye-pigment precursors of *Drosophila* was a slow and discouraging job. Tatum and I realized this was likely to be the case in most attempts to identify the chemical disturbances underlying inherited abnormalities; it would be no more than good fortune if any particular example chosen for investigation should prove to be simple chemically. Alcaptonuria was such a happy choice for Garrod, for the chemistry had been largely worked out and the homogentisic acid had been isolated and identified many years before.

Our idea—to reverse the procedure and look for gene mutations that influence known chemical reactions—was an obvious one. It followed logically from the concept that, in general, enzymatically catalyzed reactions are gene-dependent, presumably through genic control of enzyme specificity. Although we were without doubt influenced in arriving at this approach by the anthocyanin investigations, by Lwoff's demonstrations that parasites tend to become specialized nutritionally through loss of ability to synthesize substances that they can obtain readily from their hosts (*14*), and by the speculations of others as to how genes might act, the concepts on which the idea was based developed in our minds fairly directly from the eye-color work Ephrussi and I had started five years earlier.

The idea was simple: select an organism like a fungus that has simple nutritional requirements. This will mean that it can carry out many reactions by which amino acids and vitamins are made. Induce mutations by radiation or other mutagenic agents. Allow meiosis to take place, in order to produce spores that are genetically homogeneous. Grow these on a medium supplemented with an array of vitamins and amino acids. Test them by vegetative transfer to a medium with no supplement. Those that have lost the ability to grow on the minimal medium will have lost the ability to synthesize one or more of the substances present in the supplemented medium. The growth requirements of the deficient strain could then be readily ascertained by a systematic series of tests on partially supplemented media.

In addition to the above specifications, we wanted an organism well suited to genetic studies, preferably one on which the basic genetic work had already been done.

## Neurospora

As a graduate student at Cornell, I had heard B. O. Dodge of the New York Botanical Garden give a seminar on inheritance in the bread mold *Neurospora.* So-called second-division segregation of mating types and of albinos was a puzzle to him. Several of us who had just been reviewing the evidence for four-strand crossing over in *Drosophila* suggested that crossing over between the centromere and the segregating gene could well explain the result.

Dodge was an enthusiastic supporter of *Neurospora* as an organism for genetic work. "It's even better than *Drosophila,*" he insisted to Thomas Hunt Morgan, whose laboratory he often visited. He finally persuaded Morgan to take a collection of *Neurospora* cultures with him from Columbia to the new Biology Division of the California Institute of Technology, which he established in 1928.

Shortly thereafter, when Carl C. Lindegren came to Morgan's laboratory to become a graduate student, it was suggested that he work on the genetics of *Neurospora* as a basis for his thesis. This was a fortunate choice, for Lindegren had an abundance of imagination, enthusiasm, and energy and at the same time had the advice of E. G. Anderson, C. B. Bridges, S. Emerson, A. H. Sturtevant, and others at the institute who at that time were actively interested in problems of crossing over as a part of the mechanism of meiosis. In this favorable setting, Lindegren soon worked out much of the basic genetics of *Neurospora*. New characters were found, and a good start was made toward mapping the chromosomes.

Thus, Tatum and I realized that *Neurospora* was genetically an almost ideal organism for use in our new approach.

There was one important unanswered question. We did not know the mold's nutritional requirements. But we had the monograph of Nils Fries, which told us that the nutritional requirements of a number of related filamentous fungi were simple. Thus, encouraged, we obtained strains of *Neurospora crassa* from Lindegren and from Dodge. Tatum soon discovered that the only growth factor required, other than the usual inorganic salts and sugar, was the recently discovered vitamin biotin. We could not have used *Neurospora* for our purposes as much as a year earlier, for biotin would not then have been available in the quantities we required.

It remained only to irradiate asexual spores, cross them with a strain of the opposite mating type, allow sexual spores to be produced, isolate them, grow them on a suitably supplemented medium, and test them on the unsupplemented medium. We believed so thoroughly that the gene-enzyme-reaction relation was a general one that there was no doubt in our minds that we would find the mutants we wanted. We had only one worry—that their frequency might be so low that we would get discouraged and give up before finding one.

We were so concerned about the possible discouragement of a long series of negative results that we prepared more than a thousand single spore cultures on supplemented medium before we tested them. The 299th spore isolated gave a mutant strain requiring vitamin $B_6$, and the 1090th one required vitamin $B_1$. We made a vow to keep going until we had ten mutants. We soon had dozens.

Because of the ease with which all the products of a single meiotic process in *Neurospora* could be recovered, it was a simple matter to determine whether our newly induced nutritional deficiencies were the result of mutations in single genes. If they were, crosses with the original should yield four mutant and four nonmutant spores in each spore sac. They did (*15, 16*).

In this long, roundabout way, first in *Drosophila* and then in *Neurospora,* we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle. We were working with a more favorable organism and were able to produce, almost at will, inborn errors of metabolism for almost any chemical reaction whose product we could supply through the medium. Thus, we were able to demonstrate that what Garrod had shown for a few genes and a few chemical reactions in man was true for many genes and many reactions in *Neurospora.*

In the fall of 1941 Francis J. Ryan came to Stanford as a National Research Council fellow and was soon deeply involved in the *Neurospora* work. A year later David M. Bonner and Norman H. Horowitz joined the group. Shortly thereafter Herschel K. Mitchell did likewise. With the collaboration of a number of capable graduate students and a group of enthusiastic and able research assistants, the work moved along at a gratifying pace.

A substantial part of the financial support that enabled us thus to expand our efforts was generously made available by the Rockefeller Foundation and the Nutrition Foundation.

I shall leave to Tatum the task of summarizing our subsequent investigations and their results.

## One Gene—One Enzyme

It is sometimes thought that the *Neurospora* work was responsible for the one-gene–one-enzyme hypothesis—the concept that genes in general have single primary functions, aside from serving an essential role in their own replication, and that in many cases this function is to direct specificities of enzymatically active proteins. The fact is that it was the other way around—the hypothesis was clearly responsible for the new approach.

Although we may not have stated it explicitly, Ephrussi and I had some such concept in mind. A more specific form of the hypothesis was suggested by the fact that of all the 26 known eye-color mutants in *Drosophila,* there was only one that blocked the first of our postulated reactions and one that similarly interrupted the second. Thus, it seemed reasonable to assume that the *total* specificity of a particular enzyme might somehow be derived from a single gene. The finding in *Neurospora* that many nutritionally deficient mutant strains can be repaired by supplying single chemical compounds was a verification of our prediction and, as such, reinforced our belief in the hypothesis, at least in its more general form.

As I hope Tatum will point out in detail, there are now known a number of instances in which mutations of independent origin, all abolishing or reducing the activity of a specific enzyme, have been shown to involve one small segment of genetic material (*17*). To me these seem to lend strong support to the more restricted form of the hypothesis.

Regardless of when it was first written down on paper, or in what form, I myself am convinced that the one-gene–one-enzyme concept was the product of gradual evolution, beginning with Garrod and contributed to by many, including Moore, Goldschmidt, Troland, Haldane, Wright, Grüneberg, and many others (*1–4, 18*). Horowitz and his coworkers (*19*) have given it, in both forms referred to above, its clearest and most explicit formulation. They have summarized and critically evaluated the evidence for and against it, with the result that they remain convinced of its continued value.

In addition, Horowitz has himself made an important application of the concept in arriving at a plausible hypothesis as to how sequences of biosynthetic reactions might have evolved (*20*). He points out that many biologically important compounds are known to be synthesized in a stepwise manner —a process in which the intermediate compounds, as such, seem not to serve useful purposes. How could such synthetic pathways have evolved if they serve no purpose unless they are complete? Simultaneous appearance of several independent enzymes would of course be exceedingly improbable.

Horowitz proposes that the end product of such a series of reactions was at first obtained directly from the environment, it having been produced there in the first place by nonbiological reactions such as have been postulated by a num-

ber of persons, including Darwin, Haldane, Oparin, and Urey and demonstrated by Miller, Fox, and others (*21*). It is then possible reasonably to assume that the ability to synthesize such a compound biologically could arise through a series of separate single mutations, each adding successive enzymatically catalyzed steps in the synthetic sequence, starting with the one immediately responsible for the end product. In this way each mutational step could confer a selective advantage by making the organism dependent on one less exogenous precursor of a needed end product. Without some such mechanism, by which no more than a single gene mutation is required for the origin of a new enzyme, it is difficult to see how complex synthetic pathways could have evolved. I know of no alternative hypothesis that is equally simple and plausible.

### Place of Genetics in Modern Biology

In a sense, genetics grew up as an orphan. In the bginning, botanists and zoologists were often indifferent and sometimes hostile toward it. "Genetics deals only with superficial characters," it was often said. Biochemists likewise paid it little heed in its early days. They —especially medical biochemists—knew of Garrod's "inborn errors of metabolism" and no doubt were aware of their significance in the biochemical sense and as diseases, but the biological world was inadequately prepared to appreciate fully the significance of Garrod's investigations and his thinking. Geneticists, it should be said, tended to be preoccupied mainly with the mechanisms by which genetic material is transmitted from one generation to the next.

Today, happily, the situation is much changed. Genetics has an established place in modern biology. Biochemists recognize the genetic material as an integral part of the systems with which they work. Our rapidly growing knowledge of the architecture of proteins and nucleic acids is making it possible—for the first time in the history of science—for geneticists, biochemists, and biophysicists to discuss basic problems of biology in the common language of molecular structure. To me, this is most encouraging and significant.


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CURRENT PROBLEMS IN RESEARCH

# The Interpretive Cortex

## The stream of consciousness in the human brain can be electrically reactivated.


Wilder Penfield


There is an area of the surface of the human brain where local electrical stimulation can call back a sequence of past experience. An epileptic irritation in this area may do the same. It is as though a wire recorder, or a strip of cinematographic film with sound track, had been set in motion within the brain. The sights and sounds, and the thoughts, of a former day pass through the man's mind again.

The purpose of this article is to describe, for readers from various disciplines of science, the area of the cerebral cortex from which this neuron record of the past can be activated and to suggest what normal contribution it may make to cerebral function.

The human brain is the master organ of the human race. It differs from the brains of other mammals particularly in the greater extent of its cerebral cortex. The gray matter, or cortex, that covers the two cerebral hemispheres of the brain of man is so vast in nerve cell population that it could never have been contained within the human skull if it were not folded upon itself, and refolded, so as to form a very large number of fissures and convolutions (Fig. 1). The fissures are so deep and so devious that by far the greater portion of this ganglionic carpet (about 65 percent) is hidden in them, below the surface (Fig. 2).

The portion that is labeled "interpretive" in Figs. 1 and 3 covers a part of both temporal lobes. It is from these two homologous areas, and from nowhere else, that electrical stimulation has occasionally produced physical responses which may be divided into (i) experiential responses and (ii) interpretive responses.

### Experiential Responses

Occasionally during the course of a neurosurgical operation under local anesthesia, gentle electrical stimulation in this temporal area, right or left, has caused the conscious patient to be aware


The author is director of the Montreal Neurological Institute, McGill University, Montreal, Quebec.

of some previous experience (*1*). The experience seems to be picked out at random from his own past. But it comes back to him in great detail. He is suddenly aware again of those things to which he paid attention in that distant interval of time. This recollection of an experiential sequence stops suddenly when the electrical current is switched off or when the electrode is removed from contact with the cortex. This phenomenon we have chosen to call an experiential response to stimulation.

*Case examples* (*2*). The patient S.Be. observed, when the electrode touched the temporal lobe (right superior temporal convolution), "There was a piano over there and someone playing. I could hear the song you know." When the cortex was stimulated again without warning, at approximately the same point, the patient had a different experience. He said: "Someone speaking to another, and he mentioned a name but I could not understand it . . . It was like a dream." Again the point was restimulated without his knowledge. He said quietly: "Yes, 'Oh Marie, Oh Marie'! Someone is singing it." When the point was stimulated a fourth time he heard the same song again and said it was the "theme song of a radio program."

The electrode was then applied to a point 4 centimeters farther forward on the first temporal convolution. While the electrode was still in place, S.Be. said: "Something brings back a memory. I can see Seven-Up Bottling Company—Harrison Bakery." He was evidently seeing two of Montreal's large illuminated advertisements.

The surgeon then warned him that he was about to apply the electrode again. Then, after a pause, the surgeon said "Now," but he did not stimulate. (The patient has no means of knowing when the electrode is applied, unless he is told, since the cortex itself is without sensation.) The patient replied promptly, "Nothing."

A woman (D.F.) (*3*) heard an orchestra playing an air while the electrode was held in place. The music stopped when the electrode was removed. It came again when the electrode was reapplied. On request, she hummed the tune, while the electrode was held in place, accompanying the orchestra. It was a popular song. Over and over again, restimulation at the same spot produced the same song. The music seemed always to begin at the same place and to progress at the normally expected tempo. All efforts to mislead her failed. She believed that a gramaphone was being turned on in the operating room on each occasion, and she asserted her belief stoutly in a conversation some days after the operation.

A boy (R.W.) heard his mother talking to someone on the telephone when an electrode was applied to his right temporal cortex. When the stimulus was repeated without warning, he heard his mother again in the same conversation. When the stimulus was repeated after a lapse of time, he said, "My mother is telling my brother he has got his coat on backwards. I can just hear them."

The surgeon then asked the boy whether he remembered this happening. "Oh yes," he said, "just before I came here." Asked again whether this seemed like a dream, he replied: "No, it is like I go into a daze."

J.T. cried out in astonishment when the electrode was applied to the temporal cortex; "Yes doctor, yes doctor. Now I hear people laughing—my friends in South Africa!"

When asked about this, he explained the reason for his surprise. He seemed to be laughing with his cousins, Bessie and Ann Wheliow, whom he had left behind him on a farm in South Africa, although he knew he was now on the operating table in Montreal.

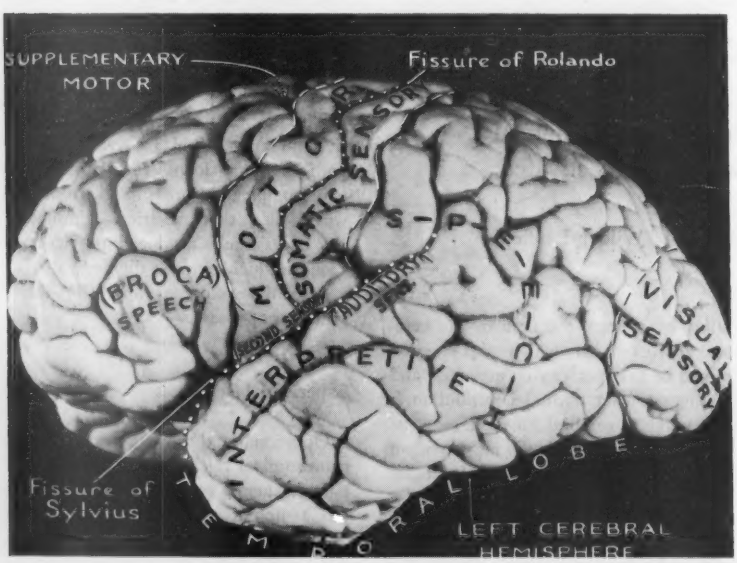



Fig. 1. Photograph of the left hemisphere of a human brain. The frontal lobe is on the left, the occipital lobe on the right. The major motor and sensory areas are indicated, as well as the speech areas and the interpretive area. [Penfield and Roberts (*18*)]

### Interpretive Responses

On the other hand, similar stimulation in this same general area may produce quite a different response. The patient discovers, on stimulation, that he has somehow changed his own interpretation of what he is seeing at the moment, or hearing or thinking. For example, he may exclaim that his present experience seems familiar, as though he had seen it or heard it or thought it before. He realizes that this must be a false interpretation. Or, on the contrary, these things may seem suddenly strange, absurd. Sights or sounds may seem distant and small, or they may come unexpectedly close and seem loud or large. He may feel suddenly afraid, as though his environment were threatening him, and he is possessed by a nameless dread or panic. Another patient may say he feels lonely or aloof, or as though he were observing himself at a distance.

Under normal circumstances anyone may make such interpretations of the present, and these interpretations serve him as guides to action or reaction. If the interpretations are accurate guides, they must be based upon previous comparable experience. It is conceivable, therefore, that the recall mechanism which is activated by the electrode during an experiential response and the mechanism activated in an interpretive response may be parts of a common inclusive mechanism of reflex recognition or interpretation.

No special function had been previously assigned by neurologists to the area in each temporal lobe that is marked

"interpretive" in Figs. 1 and 3, though some clinicians have suggested it might have to do with the recall of music. The term *interpretive cortex,* therefore, is no more than slang to be employed for the purposes of discussion. The terms *motor cortex, sensory cortex,* and *speech cortex* began as slang phrases and have served such a purpose. But such phrases must not be understood to signify independence of action of separated units in the case of any of these areas. Localization of function in the cerebral cortex means no more than specialization of function as compared with other cortical regions, not separation from the integrated action of the brain.

Before considering the interpretive cortex further, we may turn briefly to the motor and sensory areas and the speech areas of the cortex. After considering the effects of electrical stimulation there, we should be better able to understand the results of stimulation in the temporal lobes.

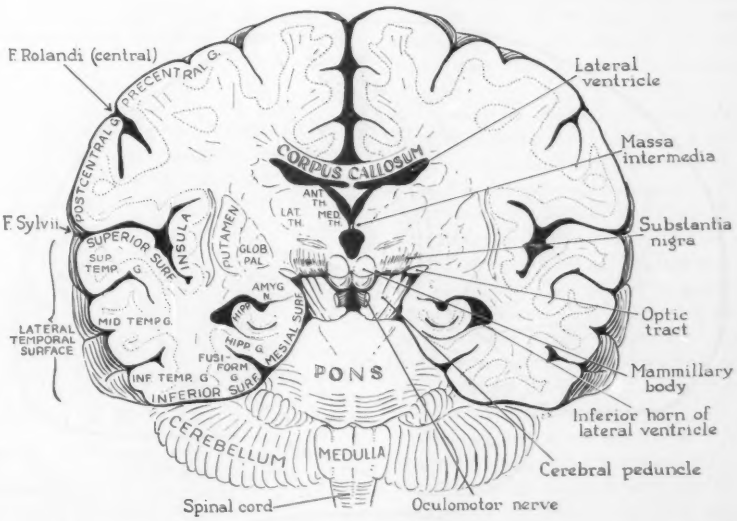
## Specialization of Function in the Cortex

Evidence for some degree of localization within the brain was recognized early in the 19th century by Flourens. He concluded from experiment that functional subdivision of "the organ of the mind" was possible. The forebrain (*4*), he said [cerebral hemispheres and higher brain stem (Fig. 4)] had to do with thought and will power, while the cerebellum was involved in the coordination of movement.

In 1861, Paul Broca showed that a man with a relatively small area of destruction in a certain part of the left hemisphere alone might lose only the power of speech. It was soon realized that this was the speech area of man's dominant (left) hemisphere. In 1870, Fritsch and Hitzig applied an electric current to the exposed cortex of one hemisphere of a lightly anesthetized dog and caused the legs of the opposite side to move. Thus, an area of cortex called motor was discovered.

After that, localization of function became a research target for many clinicians and experimentalists. It was soon evident that in the case of man, the precentral gyrus (Fig. 5) in each hemisphere was related to voluntary control of the contralateral limbs and that there was an analogous area of motor cortex in the frontal lobes of animals. It appeared also that other separate areas of cortex (Figs. 1 and 5) in each hemisphere were dedicated to sensation (one for visual sensation, others for auditory, olfactory, and discriminative somatic sensation, respectively).

Fig. 2. (Right) Photograph of a cross section of the left cerebral hemisphere [Jelgersma (*19*)]. The white matter is stained black and the gray matter is unstained. The major convolutions of the cerebral cortex and the subcortical masses of gray matter can be identified by reference to the diagram below. (Bottom) Drawing of the cross section shown at right, above, with additions. The surfaces and convolutions of the temporal lobe are identified, and the relationship of one hemisphere to the other and the relationship of the hemispheres to the brain stem and cerebellum are shown.




It was demonstrated, too, that from the "motor cortex" there was an efferent bundle of nerve fibers (the pyramidal tract) that ran down through the lower brain stem and the spinal cord to be relayed on out to the muscles. Through this efferent pathway, voluntary control of these muscles was actually carried out. It was evident, too, that there were separate sensory tracts carrying nerve impulses in the other direction, from the principal organs of special sense (eye, ear, nose, and skin and muscle) into separate sensory areas of the cortex.

These areas, motor and sensory, have been called "projection areas." They play a role in the projection of nerve currents to the cortex from the periphery of the body, and from the cortex to the periphery. This makes possible (sensory) awareness of environment and provides the individual with a means of outward (motor) expression. The motor cortex has a specialized use during voluntary action, and each of the several sensory areas has a specialized use, when the individual is seeing, hearing, smelling, or feeling.

## Traveling Potentials

The action of the living brain depends upon the movement, within it, of "transient electrical potentials traveling the fibers of the nervous system." This was Sherrington's phrase. Within the vast circuits of this master organ, potentials travel, here and there and yonder, like

meteors that streak across the sky at night and line the firmament with trails of light. When the meteors pass, the paths of luminescence still glow a little while, then fade and are gone. The changing patterns of these paths of passing energy make possible the changing content of the mind. The patterns are never quite the same, and so it is with the content of the mind.

Specialized areas in the cortex are at times active and again relatively quiet. But, when a man is awake, there is always some central integration and coordination of the traveling potentials. There must be activity within the brain stem and some areas of the cortex. This is centrencephalic integration (*5*).

## Sensory, Motor, and Psychical Responses to Cortical Stimulation

My purpose in writing this article is to discuss in simple words (free of technical terms) the meaning of the "psychical" responses which appear only on stimulation of the so-called interpretive cortex. But before considering these responses let us consider the motor and sensory activity of the cortex for a moment.

When the streams of electrical potentials that pass normally through the various areas of sensory cortex are examined electrically, they do not seem to differ from each other except in pattern and timing. The essential difference is to be found in the fact that the visual stream passes to the visual cortex and then to one subcortical target and the auditory stream passes through the auditory cortex and then on to another subcortical target.

When the surgeon stimulates the intact sensory cortex he must be sending a current along the next "piece of road" to a subcortical destination. This electrode (delivering, for example, 60 "waves" per second of 2-millisecond duration and 1-volt intensity) produces no more than elementary sight when applied to visual cortex. The patient reports colors, lights, and shadows that move and take on crude outlines. The same electrode, applied to auditory cortex, causes him to hear a ringing or hissing or thumping sound. When applied to postcentral gyrus it produces tingling or a false sense of movement.

Thus, sensation is produced by the passage inward of electrical potentials. And when the electrode is applied to the motor cortex, movement is produced by passage of potentials outward to the muscles. In each case positive response is produced by conduction in the direction of normal physiological flow—that is, by dromic conduction (*6*).

Responses to electrical stimulation that may be called "psychical," as distinguished from sensory or motor, have been elicited from certain areas of the human cortex (Fig. 6). But they have never been produced by stimulation in other areas. There are, of course, other large areas of cortex which are neither sensory nor motor in function. They seem to be employed in other neuron mechanisms that are also associated with psychical processes. But the function of these other areas cannot, it seems, be activated by so simple a stimulus as an electric current applied to the cortex.

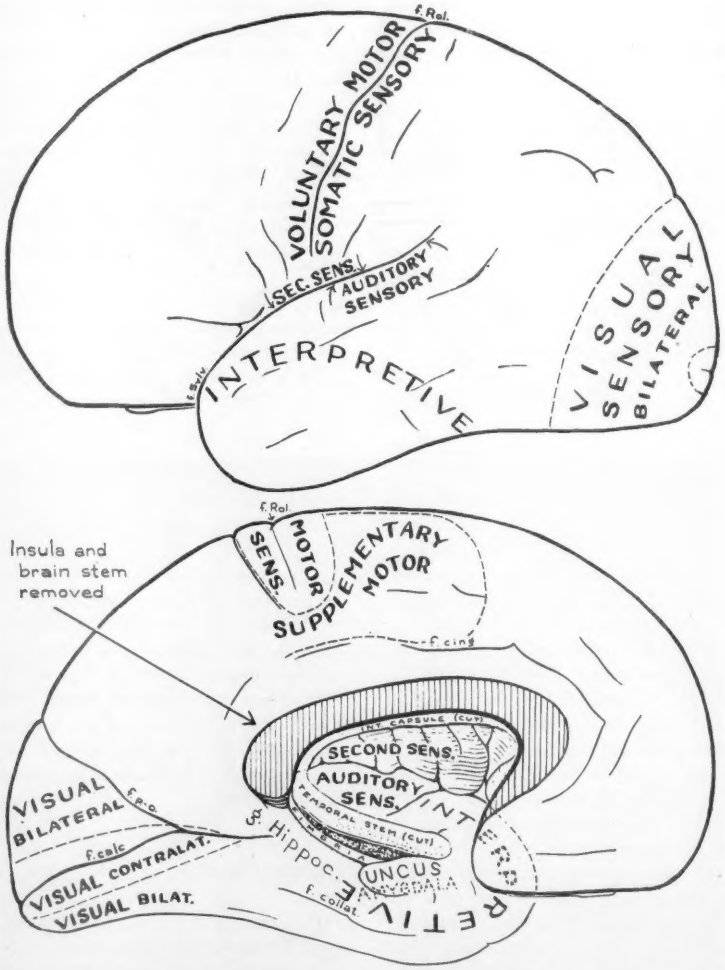



Fig. 3. The left cerebral hemisphere; the lateral surface is shown above and the mesial surface below. In the lower drawing the brain stem with the island of Reil has been removed to show the inner banks of the fissure of Sylvius and the superior surface of the temporal lobe. The interpretive cortex extends from the lateral to the superior surface of the temporal lobe. [Penfield and Roberts (*18*)]

## Dreamy States of Epilepsy

"Epilepsy" may be defined, in Jackson's words, as "the name for occasional, sudden, excessive, rapid and local discharges of grey matter." Our aim in the operations under discussion was to remove the gray matter responsible for epileptic attacks if that gray matter could be spared. When the stimulating electrode reproduced the psychical phenomenon that initiated the fit, it provided the guidance sought (*7*).

During the 19th century clinicians had recognized these phenomena as epileptic. They applied the term *intellectual*

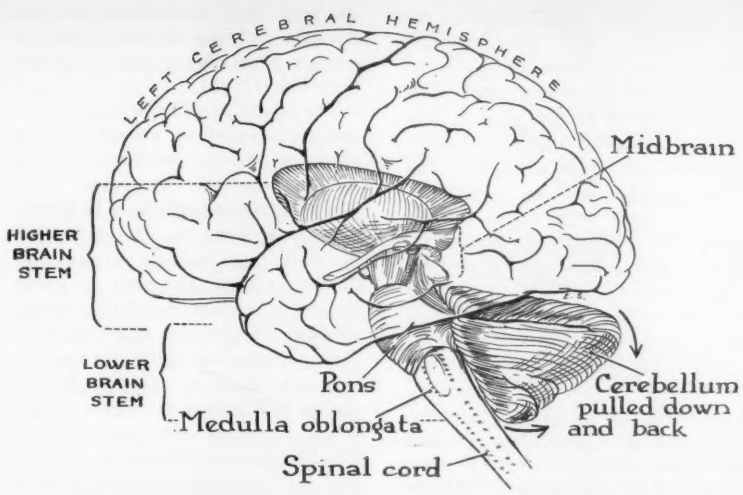



Fig. 4. Drawing of the left cerebral hemisphere, showing the higher brain stem, including the thalamus, within and the lower brain stem and spinal cord emerging below. The cerebellum is shown, attached to the lower brain stem. [Penfield and Roberts (*18*)]

*aura* to such attacks. Jackson substituted the expression *dreamy states* (see *8*). These were, he said, "psychical states during the onset of certain epileptic seizures, states which are much more elaborate than crude sensations." And again, he wrote, "These are all voluminous mental states and yet of different kinds; no doubt they ought to be classified, but for my present purpose they may be considered together."

"The state," he said, "is often like that occasionally experienced by healthy people as a feeling of 'reminiscence.'" Or the patient has "dreamy feelings," "dreams mixing up with present thoughts," "double consciousness," a "feeling of being somewhere else," a feeling "as if I went back to all that occurred in my childhood," "silly thoughts."

Jackson never did classify these states, but he did something more important. He localized the area of cortex from which epileptic discharge would produce dreamy states. His localization was in the anterior and deep portions of the temporal lobes, the same area that is labeled "interpretative" cortex in Fig. 3.

*Case example.* Brief reference may be made to a specific case. The patient had seizures, and stimulation produced responses which were first recognized as psychical.

In 1936, a girl of 16 (J.V.) was admitted to the Montreal Neurological Institute complaining of epileptic attacks, each of which was ushered in by the same hallucination. It was a little dream, she said, in which an experience from early childhood was reenacted, always the same train of events. She would then cry out with fear and run to her mother. Occasionally this was followed immediately by a major convulsive seizure.

At operation, under local anesthesia, we tried to set off the dream by a gentle electrical stimulus in the right temporal lobe. The attempt was successful. The dream was produced by the electrode. Stimulation at other points on the temporal cortex produced sudden fear without the dream. At still other points, stimulation caused her to say that she saw "someone coming toward me." At another point, stimulation caused her to say she heard the voices of her mother and her brothers (*9*).

This suggested a new order of cortical response to electrical stimulation. When the neighboring visual sensory area of the cortex is stimulated, any patient may report seeing stars of light or moving colors or black outlines but never "someone coming toward me." Stimulation of the auditory sensory cortex may cause any patient to report that he hears ringing, buzzing, blowing, or thumping sounds, perhaps, but never voices that speak. Stimulation in the areas of sensory cortex can call forth nothing more than the elements of visual or auditory or tactile sensation, never happenings that might have been previously experienced.

During the 23 years that have followed, although practically all areas of the cerebral cortex have been stimulated and studied in more than 1000 craniotomies, performed under local anesthesia, psychical responses of the experiential or interpretive variety have been produced only from the temporal cortex in the general areas that are marked "psychical responses" in Fig. 3 (*10, 11*).

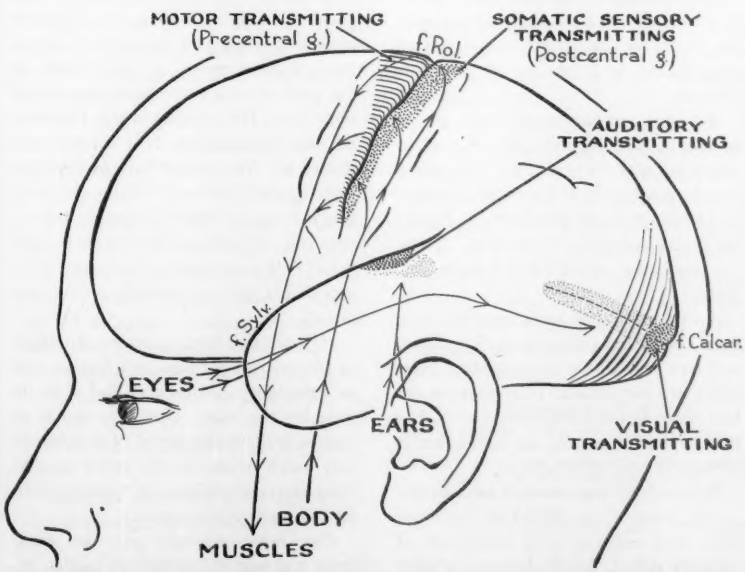



Fig. 5. Sensory and motor projection areas. The sensory areas are stippled, and the afferent pathways to them from eyes, ears, and body are indicated by entering arrows. The motor cortex is indicated by parallel lines, and the efferent corticospinal tract is indicated by emerging arrows. [Penfield and Roberts (*18*)]

## Classification

It seems reasonable to subdivide psychical responses and psychical seizures (epileptic dreamy states) in the same way, classifying them as "interpretive" or "experiential." Interpretive psychical responses are those involving interpretations of the present experience, or emotions related to it; experiential psychical responses are reenactments of past experiences. Interpretive seizures are those accompanied by auras and illusions; experiential seizures are those accompanied by auras and hallucinations.

The interpretive responses and seizures may be divided into groups (*11*) of which the commonest are as follows: (i) recognition, the illusion that things seen and heard and thought are familiar (*déjà vu* phenomenon); (ii) visual illusion, the illusion that things seen are changing—for example, coming nearer, growing larger (macropsia); (iii) auditory illusion, the illusion that things heard are changing—for example, coming near, going away, changing tempo; (iv) illusional emotion, the emotion of fear or, less often, loneliness, sorrow, or disgust.

Experiential phenomena (hallucinations) are an awareness of experiences from the past that come into the mind without complete loss of awareness of the present.

## Discussion

What, then, is the function of the interpretive cortex? This is a physiological question that follows the foregoing observations naturally.

An electrode, delivering, for example, 60 electrical pulses per second to the surface of the motor cortex, causes a man to make crude movements. When applied to the various sensory areas of the cortex, it causes him to have crude sensations of sight or sound or body feeling. This indicates only that these areas have something to do with the complicated mechanism of voluntary action or conscious sensation. It does not reveal what contribution the cortex may make, or in what way it may contribute to skill in making voluntary movement or qualify the incoming sensory streams.

In the case of the interpretive cortex, the observations are similar. We may say that the interpretive cortex has something to do with a mechanism that can reactivate the vivid record of the past. It has also something to do with a

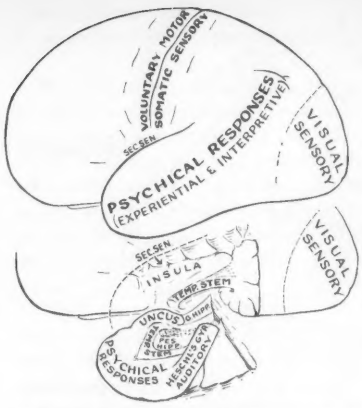



Fig. 6. The left cerebral hemisphere is shown with the temporal lobe cut across and turned down. The areas of cortex from which psychical responses have been elicited are indicated. [Penfield (*1*)]

mechanism that can present to consciousness a reflex interpretation of the present. To conclude that here is the mechanism of memory would be an unjustified assumption. It would be too simple.

What a man remembers when he makes a voluntary effort is apt to be a generalization. If this were not so, he might be hopelessly lost in detail. On the other hand, the experiential responses described above are detailed reenactments of a single experience. Such experiences soon slip beyond the range of voluntary recall. A man may summon to mind a song at will. He hears it then in his mind, not all at once but advancing phrase by phrase. He may sing it or play it too, and one would call this memory.

But if a patient hears music in response to the electrode, he hears it in one particular strip of time. That time runs forward again at the original tempo, and he hears the orchestration, or he sees the player at a piano "over there." These are details he would have thought forgotten.

A vast amount of work remains to be done before the mechanism of memory, and how and where the recording takes place, are understood. This record is not laid down in the interpretive cortex, but it is kept in a part of the brain that is intimately connected with it.

Removal of large areas of interpretive cortex, even when carried out on both sides, may result in mild complaints of memory defect, but it does not abolish the capacity to remember recent events. On the other hand, surgical removals that result in bilateral interference with the underlying hippocampal zone do make the recording of recent events impossible, while distant memory is still preserved (*12, 13*).

The importance of the hippocampal area for memory was pointed out long ago in a forgotten publication by the Russian neurologist Bechterew (*14*). The year before publication Bechterew had demonstrated the case before the St. Petersburg Clinic for Nervous and Mental Diseases. The man on whom Bechterew reported had "extraordinary weakness of memory, falsifications of memory and great apathy." These defects were shown at autopsy to be secondary to lesions of the mesial surface of the cortex of both temporal lobes. The English neurologists Glees and Griffith (*15*) reported similar defects, a half century later, in a patient who had symmetrical lesions of the hippocampus and of hippocampal and fusiform gyri on both sides.

The way in which the interpretive cortex seems to be used may be suggested by an example: After years of absence you meet, by chance, a man whose very existence you had forgotten. On seeing him, you may be struck by a sudden sense of familiarity, even before you have time to "think." A signal seems to flash up in consciousness to tell you that you've seen that man before. You watch him as he smiles and moves and speaks. The sense of familiarity grows stronger. Then you remember him. You may even recall that his name was Jones. The sight and the sound of the man has given you an instant access, through some reflex, to the records of the past in which this man has played some part. The opening of this forgotten file was subconscious. It was not a voluntary act. You would have known him even against your will. Although Jones was a forgotten man a moment before, now you can summon the record in such detail that you remark at once the slowness of his gait or a new line about the mouth.

If Jones had been a source of danger to you, you might have felt fear as well as familiarity before you had time to consider the man. Thus, the signal of fear as well as the signal of familiarity may come to one as the result of subconscious comparison of present with similar past experience.

One more example may be given from common experience. A sudden increase in the size of objects seen and in sounds heard may mean the rapid approach of something that calls for in-

stant avoidance action. These are signals that, because of previous experience, we sometimes act upon with little consideration.

## Summary

The interpretive cortex has in it a mechanism for instant reactivation of the detailed record of the past. It has a mechanism also for the production of interpretive signals. Such signals could only be significant if past records are scanned and relevant experiences are selected for comparison with present experience. This is a subconscious process. But it may well be that this scanning of past experience and selection from it also renders the relevant past available for conscious consideration as well. Thus, the individual may refer to the record as he employs other circuits of the brain.

Access to the record of the past seems to be as readily available from the temporal cortex of one side as from that of the other. Auditory illusions (or interpretations of the distance, loudness, or tempo of sounds) have been produced by stimulation of the temporal cortex of either side. The same is true of illusional emotions, such as fear and disgust.

But, on the contrary, visual illusions (interpretations of the distance, dimension, erectness, and tempo of things seen) are only produced by stimulation of the temporal cortex on the nondominant (normally, right) side of the brain. Illusions of recognition, such as familiarity or strangeness, were also elicited only from the nondominant side, except in one case.

## Conclusion

"Consciousness," to quote William James (*16*), "is never quite the same in successive moments of time. It is a stream forever flowing, forever changing." The stream of changing states of mind that James described so well does flow through each man's waking hours until the time when he falls asleep to wake no more. But the stream, unlike a river, leaves a record in the living brain.

Transient electrical potentials move with it through the circuits of the nervous system, leaving a path that can be followed again. The pattern of this pathway, from neuron to neuron along each nerve-cell body and fiber and junction, is the recorded pattern of each man's past. That complicated record is held there in temporal sequence through the principle of durable facilitation of conduction and connection.

A steady stream of electrical pulses applied through an electrode to some point in the interpretive cortex causes a stream of excitation to flow from the cortex to the place where past experience is recorded. This stream of excitation acts as a key to the past. It can enter the pathway of recorded consciousness at any random point, from childhood on through adult life. But having entered, the experience moves forward without interference from other experiences. And when the electrode is withdrawn there is a likelihood, which lasts for seconds or minutes, that the stream of excitation will enter the pathway again at the same moment of past time, even if the electrode is reapplied at neighboring points (*17*).

Finally, an electric current applied to the surface of what may be called the interpretive cortex of a conscious man (i) may cause the stream of former consciousness to flow again or (ii) may give him an interpretation of the present that is unexpected and involuntary. Therefore, it is concluded that, under normal circumstances, this area of cortex must make some functional contribution to reflex comparison of the present with related past experience. It contributes to reflex interpretation or perception of the present.

The combination and comparison of present experience with similar past experience must call for remarkable scanning of the past and classification of similarities. What contribution this area of the temporal cortex may make to the whole process is not clear. The term *interpretive cortex* will serve for identification until students of human physiology can shed more light on these fascinating findings.

### References and Notes

1. W. Penfield, *J. Mental Sci.* 101, 451 (1955).
2. These patients, designated by the same initials, have been described in previous publications in much greater detail. An index of patients (designated by initials) may be found in any of my books.
3. This case is reported in detail in W. Penfield and H. Jasper, *Epilepsy and the Functional Anatomy of the Human Brain* (Little, Brown, Boston, 1954) [published in abridged form in Russian (translation by N. P. Graschenkov and G. Smirnov) by the Soviet Academy of Sciences, 1958].
4. The forebrain, or prosencephalon, properly includes the diencephalon and the telencephalon, or higher brain stem, and hemispheres. Flourens probably had cerebral hemispheres in mind as distinguished from cerebellum.
5. "Within the brain, a central transactional core has been identified between the strictly sensory or motor systems of classical neurology. This central reticular mechanism has been found capable of grading the activity of most other parts of the brain"—H. Magoun, *The Waking Brain* (Thomas, Springfield, Ill., (1958).
6. W. Penfield, *The Excitable Cortex in Conscious Man* (Thomas, Springfield, Ill., 1958).
7. It did more than this; it produced illusions or hallucinations that had never been experienced by the patient during a seizure.
8. J. Taylor, Ed., *Selected Writings of John Hughlings Jackson* (Hodder and Stoughton, London, 1931), vol. I, *On Epilepsy and Epileptiform Convulsions.*
9. Twenty-one years later this young woman, who is the daughter of a physician, was present at a meeting of the National Academy of Sciences in New York while her case was discussed. She could still recall the operation and the nature of the "dreams" that had preceded her seizures [W. Penfield, *Proc. Natl. Acad. Sci. U.S.* 44, 51 (1958)].
10. In a recent review of the series my associate, Dr. Phanor Perot, has found and summarized 35 out of 384 temporal lobe cases in which stimulation produced experiential responses. All such responses were elicited in the temporal cortex. In a study of 214 consecutive operations for temporal lobe epilepsy, my associate Sean Mullan found 70 cases in which interpretive illusion occurred in the minor seizures before operation, or in which an interpretive response was produced by stimulation during operation. In most cases it occurred both before and during operation.
11. S. Mullan and W. Penfield, *A.M.A. Arch. Neurol. Psychiat.* 81, 269 (1959).
12. This area is marked "Hipp" and "Hipp. G" in Fig. 2 (bottom) and "g. Hippoc." and "amygdala" in Fig. 3.
13. W. Penfield and B. Milner, *A.M.A. Arch. Neurol. Psychiat.* 79, 475 (1958).
14. W. V. Bechterew, "Demonstration eines Gehirns mit Zerstörung der vorderen und inneren Theile der Hirnrinde beider Schläfenlappen," *Neurol. Zentralbl. Leipzig* 19, 990 (1900). My attention was called to this case recently by Dr. Peter Gloor of Montreal.
15. P. Glees and H. B. Griffith, *Monatsschr. Psychiat. Neurol.* 123, 193 (1952).
16. W. James, *The Principles of Psychology* (Holt, New York, 1910).
17. Thus, it is apparent that the beam of excitation that emanates from the interpretive cortex and seems to scan the record of the past is subject to the principles of transient facilitation already demonstrated for the anthropoid motor cortex [A. S. F. Grünbaum and C. Sherrington, *Proc. Roy. Soc.* (*London*) 72B, 152 (1901); T. Graham Brown and C. S. Sherrington, *ibid.* 85B, 250 (1912)]. Similarly subject to the principles of facilitation are the motor and the sensory cortex of man [W. Penfield and K. Welch, *J. Physiol.* (*London*) 109, 358 (1949)]. The patient D.F. heard the same orchestra playing the same music in the operating room more than 20 times when the electrode was reapplied to the superior surface of the temporal lobe. Each time the music began in the verse of a popular song. It proceeded to the chorus, if the electrode was kept in place.
18. W. Penfield and L. Roberts, *Speech and Brain Mechanisms* (Princeton Univ. Press, Princeton, N.J., 1959).
19. G. Jelgersma, *Atlas anatomicum cerebri humani* (Scheltema and Holkema, Amsterdam).

# News of Science

## Congress Dissatisfied with the Executive's Role in Science

Problems in the administration of science are causing a widening breach between the executive and legislative branches of the Government. This is perhaps one of the most significant matters brought out by the latest Congressional hearing on bills S.676 and S.586 for the creation of a Federal Department of Science and Technology. On 28 May the Subcommittee on Reorganization and International Organization of the Senate Committee on Government Operations, which is under the chairmanship of Senator Hubert H. Humphrey (D-Minn.), met to receive testimony supplemental to that heard during its April sessions, and to consider S.1851, a bill that was introduced on 5 May to provide that a Commission on a Department of Science and Technology be formed to study the need for such a department. The study commission bill resulted from recommendations offered at the April meeting.

As had been pointed out at the preceding hearings, the objective of the committee is to "place emphasis" upon the need for reorganization of federal science activities and to promote better centralization and coordination of federal science programs and operations. In his opening statement, Senator Humphrey stressed that bills S.676 and S.586 should be considered merely as an approach to the problems involved and that they in no way represent the conclusions of the committee. Through its hearings, the committee hopes to develop testimony that will lead to the approval of legislation to accomplish its objectives.

### Waterman's Testimony Shows Issue

Congress' dissatisfaction with the executive department's role in science legislation emerged clearly when committee members commented on testimony by Alan T. Waterman, director of the National Science Foundation, who opposes both the new science department and the study commission. To support his position, Waterman referred to the measures that have been taken by the President since Sputnik to strengthen science and its use in the Federal Government.

He mentioned the President's action in appointing James F. Killian as special assistant for science and technology. He pointed out that the reorganization and reassignment of the Science Advisory Committee to report to the President "has been an impressive step" toward assisting the Government in the solution of some of the most urgent problems having to do with science and technology. He observed that other actions of significance include the reinstatement of the Office of the Science Adviser in the Department of State and the appointment of scientific attachés; the enactment of the Department of Defense Reorganization Act, which included the setting up of the Office of Director of Research and Engineering; and the passage of legislation creating the National Aeronautics and Space Administration and the National Aeronautics and Space Council, presided over by the President. Finally, he referred to the President's establishment of the Federal Council for Science and Technology as a further step that will promote closer cooperation among government agencies with research and development programs.

At the close of this summary, the following exchange took place between Waterman and Humphrey.

Waterman: "I believe that this council will be an effective mechanism for achieving the desired objectives, particularly because of the fact that the chairman of the Council, Doctor Killian, is also Special Assistant to the President and brings directly to the President those matters which need to be considered by the President personally."

Humphrey: "What does this wonderful council ever say to us?"

Waterman: "Well, as I take it, Mr. Chairman, the council would make recommendations to the President as to the allocation of responsibilities among the Departments and Agencies in matters of coordination, and thereafter, each agency would deal with the Congress with respect to the program so allocated. It would have the strength of agreement among the agencies and the President's decision so that each agency would then carry out its part and the Congress would understand that full coordination had been achieved."

Humphrey: "Let me tell you what my view of it is. I understand the reports of those councils are Executive Privilege reports. Members of Congress never see them. We see the reports as they are filtered, strained, restrained and constrained. . . . We see them after they have been given a working over by the Bureau of the Budget and everybody else. . . .

"I use this opportunity . . . to protest this kind of treatment and withholding of privileged material. It just makes it impossible for a committee of Congress to ever get full information upon which to take constructive action. . . .

"I am going to say here that if we can't be trusted with this material, we ought not to be elected to public office, and I don't think some of the people that are appointed are any more trustworthy than some of us who have been elected."

### Specialists Refuse to Testify

Congressional irritation is not limited to the inaccessibility of executive branch background reports. A number of Senators feel particular pique over the refusal of various specialists on Executive Office commissions and councils to testify before investigating committees on the grounds that it would be inappropriate for Presidential advisers to do so. For this reason, a letter from Killian, written on 31 March, was introduced into the hearing record. It read in part:

"I appreciate very much being invited to testify at the hearings to be held by the Senate Committee on Government Operations and Bill S.676 to create a Department of Science and Technology.

"Under normal circumstances, I would welcome the opportunity to testify. Under present circumstances, I believe it to be inappropriate for me to do so because of my advisory functions here in the White House."

### Congressional Concern Summarized

Senator Humphrey defined the Congressional concern when he made the following remarks to the committee.

"I have a feeling that only when these councils in the Executive Office of the President share frankly with legislative representatives—openly, candidly, cooperatively—will there be real cooperation and coordination of the federal science activities. . . . When there isn't that kind of esprit de corps between the two branches, executive and legislative, and a legislative subcommittee has to dig around and do its own investigation and sleuthing, that is when the trouble starts."

Ernest S. Gruening (D-Alaska) is also worried about what he described at the hearings as "the gaps that exist between the executive branch of the Government and the Congress." In referring to the situation, he used the terms "dichotomy" and "lack of entente."

Still another participant, Ralph Yarborough (D-Tex.), added his note of protest by pointing out that the success of the executive branch's science advisory bodies depends in large measure upon the personal rapport between the President and his science adviser. Emphasizing that these "organs" exist solely at the will of the President, Yarborough asked: "Will they function effectively, or even exist, when the climate of opinion changes or when the White House has a new occupant?"

Yarborough's reference to rapport with the science adviser raised a point that has especially disturbed some Congressmen: the great reliance that has been placed on Killian personally. Almost every witness at the recent hearings, whether for or against the bills being considered, referred to his special role. Congressional spokesmen noted that on the very day that the committee was discussing Killian's unusual importance, his resignation was announced.

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## Retired Officers' Role in Defense Industry To Be Studied

In early July a special subgroup of the Armed Services Committee of the House of Representatives will look into the role of retired officers in the defense industry. The group, the subcommittee for special investigations, headed by Representative F. Edward Hébert (D-La.), will examine charges recently made that former military personnel who, on retirement, take jobs with Defense Department contractors in industry are unduly influencing the placement of contracts. The matter has come up in past years, but no conclusive action has been taken. It came up again early this month when Representative Alfred E. Santangelo (D-N.Y.) attempted to amend the Department of Defense appropriation bill by adding a provision that would prohibit the awarding of any contracts to companies which employ military officers who have been retired for less than 5 years. Two votes were taken on Santangelo's proposal. The result of the first —a standing vote—was 131 to 130 against the amendment. Following this Santangelo called for a "teller" vote, which allows for greater accuracy. This resulted in 125 "ayes" and 147 "noes." (The discrepancy in the total number of votes was the result of changes in the number of House members on the floor in the course of the voting.)

The following day another approach to the problem was initiated by Representative Charles Bennett (D-Fla.) when he introduced a bill (HR 7555) to prohibit the employment by industrial concerns which do defense work for the Government of persons who had worked in the defense establishment. Bennett had introduced similar bills in both the 82nd and 83rd congresses, but there had been little response.

### Problem is Complex

The question that the special investigation committee will study is this: What is involved when a retired officer takes a job with a firm that does a great deal of defense work? In many cases the individual involved simply goes from one side of the table to the other. During his military services a man may be the contracting officer who orders certain items of equipment for his base or unit. He may, on retirement, be offered a selling position by the firm with which he had had dealings.

The House debate brought out two conflicting views of the role that such ex-officers may have if they accept jobs with defense contractors. Santangelo, speaking for his amendment, cited two major points. "Persons within the Department [of Defense] who may be looking forward to possible employment with a certain organization after retirement can display partiality and favoritism without ever realizing it. Further, prominent military figures in retirement can have a great influence over their former subordinates who are still in the Department. Contact at social and professional gatherings between active and retired officers can provide a perfectly natural setting for influence and favoritism." After citing very large increases in capital investment on the part of three airplane companies since 1952, Santangelo asked his fellow members this question: "Why do these industrial contractors engage or hire retired military or naval officers at inordinate salaries? Is it because of their technical knowledge or is it because of their relationship with their former colleagues or former subordinates who are at the levers of control?"

As the vote indicates, more than half the House members were opposed to legislation designed to prohibit officers from taking jobs in industry after retirement. The case for the opposition was put by Representative Samuel S. Stratton (D-N.Y.): "I think there are two points that ought to be borne in mind by the House. In the first place, we are denying to our defense industries, if this amendment goes into effect, the services and assistance of the very people who have had the most experience in the fields of weapons and related matters. . . . If this amendment were to go through in this extreme form, we would actually be jeopardizing our own national defense. We would be throwing out the baby with the bath. Secondly, this House not too long ago adopted the so-called 'hump' bill for the Navy, and we are expected soon to be presented with a similar piece of legislation for the Air Force, under which valuable officers in the higher ranks will be forced to retire before their time with a lesser return in retirement pay. If this amendment were to be adopted, therefore, we would be foreclosing to these loyal officers, many with families still to educate, the chance of entering certain fields of gainful employment after their forced retirement, particularly those fields where they are best qualified and best able to serve.

### Obligation to Whom?

More complex issues are also involved, however. For the officers concerned, especially the graduates of the service academies, the problem becomes a very difficult one. During the debate that followed Santangelo's proposal, a case in point was offered by another member. He told of a colonel currently in service who is an expert in nuclear energy. All of the officer's higher schooling had been paid for by the Government, from West Point through graduate work at the Massachusetts and California institutes of technology. The colonel had served for 20 years and was entitled to retirement at any time. Or, if he chose, he could stay on and complete 30 years' service. The colonel put his problem this way. "I have a family of four youngsters all going to high school at the present time, about ready to go to college. I have the opportunity to retire and to go to work for one of the larger companies at a salary twice what I am now receiving. To whom do I owe the obligation? Do I owe it to the country who gave me my education, . . . who sent me to MIT and to CalTech, and for whom I have worked through the years? Or do I owe the obligation to my family, to take my pension and go out into newer fields where I can double my salary?"

### Debate May Be Long

Because of the complexity of the retired-officer problem and the fact that there are strong arguments on both sides, the Hébert investigation may be long and involved. Apart from the main issue, there is a possibility that another matter, currently in the news, will impinge on the investigation. This is the "munitions lobby," on which President Eisenhower has recently commented. In

remarks to several Senators, the President has indicated that he feels that "something other than the strict military needs of this country" is having influence on the decisions that determine national defense policy. If this matter, which in the opinion of some commentators has an obvious relationship to the role of retired officers in the defense industry, is made a part of the Hébert investigation, July may be a very noisy month in Washington.

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## Senate Votes Space Agency $485 Million for Fiscal 1960

By a vote of 88 to 1, the Senate has passed an authorization bill (HR 7007) that exactly conforms to President Eisenhower's request for funds for the National Aeronautics and Space Administration. A total of $485 million is authorized by the bill for the space agency's operations during fiscal year 1960. John E. Stennis (D-Miss.), chairman of the NASA authorization subcommittee, said the amount would probably be the smallest of the yearly space authorization bills to come before Congress in the next 5 to 10 years. The Senate action restored a number of cuts made in the bill by the House of Representatives. Funds amounting to $4.75 million, which NASA requested for a rocket-fuel research center, had been deleted by the lower chamber on the grounds that NASA officials did not have a definite site in mind for the center. The Senate committee restored the funds after hearing that a decision on the matter would be made within 3 months. In passing the bill, the Senate also added a provision requiring the space agency to notify both the House's Science and Astronautics Committee and the Senate's Aeronautical and Space Science Committee before any research and development project costing $250,000 or more is begun.

Another lopsided vote—392 to 3—resulted in House approval of the authorization bill for the Defense Department. The bill, which provides approximately $39 billion for the armed services, will need Senate approval before it becomes effective. The total provided was about $400 million less than the President requested in his budget and about $1 billion less than was voted for fiscal 1959. In making its authorization, the House of Representatives followed the recommendations of its Defense Appropriations subcommittee. In its report the committee said it "is not happy over the prospect of being in second place to the U.S.S.R. in the highly significant ICBM field." One of the committee's recommendations was for $85 million "as a down payment" for another eight squadrons of Atlas ballistic missiles.

In another appropriation action, the Joint Congressional Committee on Atomic Energy has approved a bill to provide the Atomic Energy Commission with $180 million for fiscal year 1960. The greater part of this amount—$165 million—is for plan acquisition and construction. Another provision increases the funds for research on atomic fallout from $2 million, which the commission requested, to $3 million. The congressional committee also extended for another 5 years a compulsory patent-licensing provision that prevents a private company from obtaining monopolistic control of the atomic-energy industry by restricting the use of any major discovery its employees might make while doing work contracted for by the AEC.

## Progress in Mental Health Care

The National Association for Mental Health reports that resident patients in state and county mental hospitals stood at 545,000 on 31 December 1958, compared to 548,000 at the end of 1957, a reduction of approximately one-half of 1 percent. Admissions in 1958 were 210,000, compared to 195,000 in 1957—a rise of about 8 percent. The net fall in the resident population of the state and county hospitals in the face of the steep increase in admissions indicates that more patients are getting more treatment. However, the association's annual report warns that it is primarily the new admissions that are being helped and discharged. The great majority of the old patients are getting little or no treatment at all.

When rated according to minimum standards set by the American Psychiatric Association, few mental hospitals are shown to be giving their patients the treatment they need. Of the 228 mental hospitals and institutions inspected by the American Psychiatric Association by the end of 1958, only 34 were approved. Sixty-six had been given only conditional approval and 109 were disapproved. Reports on the remaining 19 had not yet been released at the time the mental health association's annual review was being written.

## Preservation of Educational Standards During Teacher Shortage

A nationwide program of experiments on ways of preventing deterioration of education resulting from the mounting shortage of college teachers by improving the use of available teaching resources has been described in a report issued by the Fund for the Advancement of Education (477 Madison Ave., New York 22). The study discusses the following innovations: (i) more responsibility to students for their own learning; (ii) regular use of television, films, self-teaching machines, and other technological devices; (iii) teaching students in large groups, which ranged as high as from 100 to 400; (iv) use of graduate and undergraduate teaching assistants or part-time faculty members; (v) streamlining the curriculum to reduce proliferation and duplication of courses.

The experiments reviewed in the report were supported by the Fund in 1956 and 1957 to make better use of college teachers' time, talents, and skills. The report was submitted to the Fund by a group of college and university administrators who form the Committee on Utilization of College Teaching Resources. The committee was established in 1956 to formulate the program of experiments. In the 2 years, the fund has made 62 grants totaling $994,845 to 48 colleges and universities.

## News Briefs

The Office of Science Information Service of the National Science Foundation has started a series of studies of national scientific and technical communication systems that are intended to serve as an information base for the development of future cooperative programs. Grants have been made to examine national systems as follows: Poland, John L. Mish, through the New York Public Library; Japan, George H. Kerr, through the Pacific Science Board; Indonesia, John O. Sutter, through the Pacific Science Board. The program will be expanded to include other areas of the world. Plans for publication resulting from these studies will be announced later.

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A 6200-volume set of books on entomology has been acquired by the D. H. Hill Library at North Carolina State College. The collection, purchased from Frederick F. Tippmann, an engineer and amateur ornithologist, had a market value of $60,000 and included many rare volumes. This acquisition, according to college officials, makes the Hill Library the foremost institution in the Southeast in entomological material and places it among the leading institutions in the nation in this field. The Tippmann collection was described as "one of the few remaining great private entomological libraries."

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The presidents and top scientists of 20 Rocky Mountain colleges and universities have joined together to form a new cooperative research corporation, Asso-

ciated Rocky Mountain Universities, Inc. Every public and private institution in the eight mountain states that offers a master's degree in science is a participant in ARMU. The corporation is designed to attract new scientific installations to the Rocky Mountain area by offering the cooperative efforts of its members to the solution of the scientific and management problems involved.

* * *

An agreement between the Department of Defense and the National Aeronautics and Space Administration, making available DOD's Industrial Security Program to NASA, has eliminated the need for the civilian space agency to establish a similar program. The agreement authorizes DOD to act on behalf of the NASA in security matters relating to contractors.

* * *

The International Atomic Energy Agency issued a directory of power reactors now in operation or under construction in various parts of the world. This is the agency's first major scientific publication; directories of other types of reactors are under preparation. In all, 36 power reactor projects have been included in the directory, 15 in the United States, eight in the United Kingdom, four each in France and the U.S.S.R., and one each in Belgium, Canada, Czechoslovakia, Germany (Federal Republic), and Sweden. In some cases a project comprises more than one reactor. The reactors have been grouped in six categories, according to the coolant used.

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A bust of Ales Hrdlicka (1869–1943), world-famous anthropologist who was associated with the Smithsonian Institution for 40 years, was presented recently to the Smithsonian's National Museum by Miloslad Ruzek, ambassador of the Czechoslovak Republic to the United States. The gift was made on behalf of several educational and cultural groups of Czechoslovakia as a memento of the recent observances in that country marking the 15th anniversary of Hrdlick's death and the 90th anniversary of his birth.

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The federal budget now allocates some $6.8 billion to research on weapons and less than 4 percent of that amount to all medical research, according to Senator Richard Neuberger in an address to the National Conference on World Health in Washington last month.

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The U.S. Office of Education, Washington 25, D.C., has announced publication of its second annual review and digest of state legislation affecting higher education. The report was prepared by the Division of Higher Education primarily for use in planning future programs and budgets for colleges and universities. The new publication, *Survey of State Legislation Relating to Higher Education*, covers the period 1 July 1957 to 30 June 1958.

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As the final part of its survey of the over-all United States research and development effort during 1953–54, the National Science Foundation has released *Scientific Research and Development in Colleges and Universities—Expenditures and Manpower, 1953–54*. The 173-page publication may be obtained for $1 from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C.

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The National Aeronautics and Space Administration has formed the Committee on an Equatorial Range to study the need for, and the technical feasibility of, an equatorial launching site. John P. Hagen, assistant director for program coordination in the Office of Space Flight Development, is chairman of the new group.

## Scientists in the News

The National Academy of Sciences–National Research Council recently announced the election of the following foreign associates.

V. A. AMBARTSUMIAN, director of the Burakan Observatory, Erevan, Soviet Armenia.

Sir EDWARD C. BULLARD, assistant director of research, department of geodesy and geophysics, Cambridge University, England.

MAX HARTMANN, Max Planck–Institute für Biologie, Tübingen, Germany.

W. V. HODGE, Lowndean professor of astronomy and geometry, Cambridge University, England.

NIELS BOHR, director of the Institute for Theoretical Physics at the University of Copenhagen, Denmark, and 1922 Nobel Prize winner, delivered an address at the dedication of the John Jay Hopkins Laboratory for Pure and Applied Science of the General Dynamics Corporation, on 25 June. The new laboratory is in San Diego, Calif.

The Gravity Research Foundation has announced the winners of its annual awards for the five best essays on gravity.

J. WEBER, professor at the University of Maryland, received the first award of $1000.

M. E. ROSE, chief physicist at Oak Ridge National Laboratory, received the second award of $300.

H. BONDI, professor at the University of London, King's College, received the third award of $200.

HUSEYIN YILMAZ, Institute for Advanced Study, Princeton, N.J., received the fourth award of $150.

MAURICE ALLAIS of Paris, received the fifth award of $100, and O. COSTA DE BEAUREGARD, also of Paris, earned an honorable mention.

*Medicine and the Stars*, one of the first Japanese technical publications on space medicine, has been dedicated to HUBERTUS STRUGHOLD, professor of space medicine and adviser for research at the School of Aviation Medicine, Randolph Air Force Base, Tex. The book covers a great deal of the pioneer research work that Strughold and his colleagues began in 1947.

The American Academy of Arts and Sciences, at its 179th annual meeting, elected 113 new fellows from 19 states of the United States, and 21 foreign honorary members from 11 countries. Four women were included in this number, one of them, ANNA FREUD of London, being the fourth female foreign honorary member in the history of the academy. At the same meeting, officers for the academy for 1959–60 were elected. KIRTLEY F. MATHER, emeritus professor of geology at Harvard University, was reelected president for another year. The new foreign scientist members, including Dr. Freud, are as follows.

*Mathematics.* A. N. KOLMOGOROV, Academy of Sciences, Moscow, U.S.S.R.; JEAN LERAY, Collège de France, Paris.

*Physics.* MAX BORN, Edinburgh University, Bad Pyrmont, Germany; Sir WILLIAM L. BRAGG, Royal Institution, London, England.

*Astronomy.* MARCEL G. J. MINNAERT, University of Utrecht, Utrecht, Netherlands.

*Engineering sciences.* GEORGE K. BATCHELOR, University of Cambridge, Cambridge, England.

*Biophysics and biochemistry.* Sir JOHN C. ECCLES, Australian National University, Canberra; DAVID KEILIN, Cambridge University, Cambridge, England.

*Botany and bacteriology.* HITOSHI KIHARA, National Institute of Genetics, Misima, Japan.

*Zoology.* JEAN BRACHET, University of Brussels, Brussels, Belgium; PETER B. MEDAWAR, University College, London, England.

*Medicine.* Sir GEORGE W. PICKERING, Oxford University, Oxford, England.

*Social relations.* ANNA FREUD, London, England.

GLENN T. SEABORG, chancellor of the University of California, Berkeley, and Nobel laureate, has been made an honorary fellow of the Chemical Society of Great Britain, the highest honor that can be conferred on a foreign colleague.

LUIGI M. VENANZI of Oxford University, England, will give a series of chemistry lectures at Rutgers University, 20 July–14 August. His topic will be "Cooordination and Organo-Metallic Compounds."

NICHOLAS FUSCHILLO, head of the Magnetics and Semiconductor Branch at Franklin Institute, Philadelphia, has joined CBS Laboratories, Stamford, Conn., as head of the solid state physics department. ALFRED E. KASPAUL, with CBS since 1957, has been appointed technical manager of Solid State Physics Laboratories.

J. H. PIDDINGTON, radio astronomer with the Division of Radiophysics of the Commonwealth Scientific and Industrial Research Organization, Melbourne, Australia, has received the Royal Society of New Zealand's T. K. Sidey (Summertime) Award, for a theoretical explanation of heating in the atmosphere of the sun.

W. W. GRIGORIEFF, chairman of the University Relations Division of the Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn., has returned from a year's service in the Exchange and Training Division of the International Atomic Energy Agency, Vienna, Austria.

WILLIAM S. JOHNSON, Homer Adkins professor of chemistry at the University of Wisconsin, has been named head of Stanford University's chemistry and chemical engineering department, effective in 1960. He will succeed GEORGE S. PARKS, who will become emeritus head this year.

CARL DJERASSI, professor of chemistry at Wayne State University, on leave in Mexico City, has been appointed professor of chemistry at Stanford, effective in September, but will remain on leave for another year. He is vice president for research of Syntex, S.A., hormone manufacturing firm in Mexico City.

Recent honorary degrees include the following.

DANA W. ATCHLEY, professor emeritus of clinical medicine at Columbia University, from Columbia University.

LLOYD V. BERKNER, president of Associated Universities, Inc., from Columbia University.

ARTHUR H. BILL, retired head of Western Reserve University Medical School's department of obstetrics, from Marietta College.

DEREK E. DENNY-BROWN, professor of neurology at Harvard University and director of neurological research at Boston City Hospital, from Wayne State University.

VANNEVAR BUSH, chairman of the corporation of the Massachusetts Institute of Technology, from Boston University.

JAMES B. FISK, president of Bell Telephone Laboratories, from Newark College of Engineering.

DONALD A. GLASER, professor of physics at the University of Michigan, from Case Institute of Technology.

LLOYD A. HALL, technical director, the Griffith Laboratories, Inc., Chicago, from Howard University, Washington, D.C.

NEWMAN H. HALL, chairman of the Yale University department of mechanical engineering, from Marietta College.

ALFRED B. JEPSON, senior group adviser for Boeing Aircraft Corporation, from Case Institute of Technology.

JOHN W. JORDAN, technical director of Baroid Division of National Lead Company, from Marietta College.

MERVIN J. KELLY, retired chairman of the board of Bell Telephone Laboratories, from Case Institute of Technology.

JAMES C. KONEN, vice president of Archer-Daniels-Midland Company, Minneapolis, Minn., from North Dakota Agricultural College.

CHAUNCEY D. LEAKE, assistant dean at Ohio State University College of Medicine, from Kenyon College.

MURRAY GELL-MANN, professor of physics at California Institute of Technology, from Yale University.

ERNST MAYR, professor of zoology at Harvard University, from Yale University.

ROBERT F. MEHL, head of the department of metallurgy and dean of the Graduate School of Carnegie Institute of Technology, from Case Institute of Technology.

FAIRFIELD OSBORN, president of the Conservation Foundation and the New York Zoological Society, from Kenyon College.

M. J. RATHBONE, president of Standard Oil of New Jersey, from Marietta College.

DAVID B. STEINMAN, bridge engineer, from Syracuse University.

ERNST WEBER, president of the Polytechnic Institute of Brooklyn, from Newark College of Engineering.

JOHN R. HELLER, director of the National Cancer Institute of the U.S. Public Health Service, has received the 1958 Wien Award for his outstanding contributions to cancer cytology.

RALPH S. HALFORD has resigned as chairman of Columbia University's department of chemistry to serve as provost for projects and grants, a newly established office. He will continue to teach and conduct research.

KUNDAN S. SINGWI, head of the theoretical physics and applied mathematics division at the Atomic Energy Establishment of India, Trombay, has been appointed resident research associate at the Argonne National Laboratory for 2 years.

## Recent Deaths

HARRY BAUM, New York; 76; chairman of the department of electrical engineering at City College from 1935 until his retirement in 1949; served as engineering and technical adviser to the Board of Higher Education; 6 June.

HERBERT P. EVANS, Madison, Wis., 59; chairman of the University of Wisconsin Extension Division's department of mathematics since 1945; taught in the mathematics department of the university's College of Letters and Science, and was in charge of the elementary mathematics program for students there and in the College of Engineering; 2 June.

JAMES L. GAMBLE, Brookline, Mass.; 75; professor of pediatrics at Harvard University Medical School from 1929 until his retirement in 1950; instructor in pediatrics at the Johns Hopkins University Medical School, 1915–22; former president of the American Pediatric Society; 28 May.

JOHN M. HARGREAVES, Portland, Ore.; 58; former deputy surgeon general of the Air Force.

AMBROSE LANSING, Apache Junction, Ariz.; 67; anthropologist and egyptologist; curator emeritus of art of the Metropolitan Museum of Art in New York; 28 May.

GEORGE H. LOFTUS, Ridgewood, N.J.; 67; vice president of the Radium Chemical Company, Inc., New York; developed several new types of radium applicators for medicinal uses, including one for the prevention and treatment of deafness in children; 28 May.

Msgr. JOHN L. McNULTY, South Orange, N.J.; 60; president of Seton Hall University since 1949; directed the establishment of Seton Hall College of Medicine and Dentistry in 1956; 28 May.

C. B. POLLARD, Gainesville, Fla.; 59; professor of chemistry at the University of Florida, and a specialist in scientific crime detection and toxicology; 31 May.

CHARLES S. SWOPE, West Chester, Pa.; 60; president of West Chester State Teachers College since 1935; 1 June.

# Book Reviews

**Speech and Brain-Mechanisms.** Wilder Penfield and Lamar Roberts. Princeton University Press, Princeton, N.J., 1959. xiii + 286 pp. Illus. $6.

Among distinctions that differentiate man from his fellow creatures, probably the most spectacular and certainly the most important in relation to man's capacity to accumulate and benefit from knowledge is that of language and speech. This monograph by Wilder Penfield and Lamar Roberts represents the most substantial body of data and plausible conceptual contributions yet available for understanding the internal brain mechanisms relating to speech and language.

In many respects the book is more than a contribution of these two authors, as they freely acknowledge. This is evident not only from the contributions of persons who helped directly with the materials of the book itself but, in an even more cogent sense, from the contributions of Herbert H. Jasper, neurophysiologist, who has made a particular contribution to the authors' conceptions of thalamocortical functional relations, mechanisms of epilepsy, and other problems; Preston Robb, neurologist, who collaborated with Penfield in earlier studies concerning language and speech mechanisms; and Brenda Milner, psychologist, who collaborated in studies of perceptual and memory mechanisms. All of these individuals are part of the dedicated and expert staff of the Montreal Neurological Institute. Another contributor is Joseph Klingler, professor at the University of Basel, who prepared for this book a series of anatomical demonstrations which display advantageously the fiber connections linking cortex and thalamus. Eleanor Sweezey has made useful companion drawings of these dissections.

*Speech and Brain-Mechanisms* is a triumph in terms of its effective revelation of very complex and only slightly understood brain mechanisms in a form suitable for a general as well as a professional audience. The general conclusions of the monograph were given by Penfield in the Vanuxem Lectures at Princeton in 1956. Both authors are acutely aware of their opportunity to explain these fascinating and important observations and conclusions to as wide an audience as possible. Patients, shielded from pain by local anesthesia and having large areas of their brain exposed for electrical recording and stimulation, participate actively in the operative experience. They contribute subjective as well as objective evidence which is essential for an identification of sensory and motor fields. More particularly for the development of this study, they respond to command by counting or speaking while various local regions of the brain are explored with a weakly exciting electrical current that may interrupt their speech, interfere with their ability to match concepts with language, and evoke other alterations in the stream and content of consciousness, experience, and performance.

The patients were operated on for therapeutic reasons usually related to cortical atrophy associated with epilepsy. Brain-mapping was performed to supplement other diagnostic procedures for localization of the epileptic focus, to identify within the exposed field the primary motor and sensory projection areas, and to reveal as much as possible about the extent and character of speech areas. Of course, a thorough appraisal of speech capabilities was made prior to the surgical intervention and during the course of recovery. It is interesting to note that aphasia, when it occurred postoperatively, was only transient, except in the case of five patients all of whom continued to have seizures. Transient postoperative aphasia may appear a few days after the operation. The authors refer to this as "neuroparalytic edema," although they point out that it is not always paralytic but may be associated with local seizure activity, and that the time course is unusual for edema.

Evidence derived from stimulation and cortical excision resulted in the identification of three large cortical speech areas within the dominant hemisphere, exclusive of the central sensorimotor region. The largest speech area is located midway between the parietal, occipital, and temporal regions and is considered to be the most essential of the three. A second speech area lies in front of the motor face region, the classical Broca's area; this is definitely dispensable in some patients. The third, a superior or supplementary motor area, lies mainly on the upper part of the medial surface of the dominant hemisphere, just in front of the motor region. This most dispensable region is one in which Penfield had previously discovered other motor functions. The sensori-motor area surrounding the central sulcus is actually contiguous with each of these three speech areas and itself plays an essential role in the articulation of speech. In contrast with the other speech areas, however, it has nearly equivalent representation in the nondominant hemisphere, and on this account the authors do not depict the sensori-motor cortex in their illustrations of localization of speech functions.

Other parts of the left hemisphere—primarily the frontal and occipital poles—have been stimulated without affecting speech. However, the number of stimulations was not sufficient to be statistically significant. A few cortical excisions which lay predominantly, if not entirely, outside the major speech areas and yet were followed by transient aphasia have been reported. "It seems, as [Hughlings] Jackson stated, that any acute lesion to any gross part of the left hemisphere will produce some disturbance in speech. It should be mentioned that this includes disease of the anterior and posterior cerebral arteries as well as of the middle cerebral." Despite decades of continuing conscientious effort, the authors are careful to point out that they have relatively little knowledge of the effects that might be obtained from stimulating gray matter hidden within the folds of cortical sulci but can only assume "that the convolutions have the same function deep in the fissures as they do on the convexity."

More than 20 years ago Penfield came to the realization that "the indispensable substratum of consciousness lies outside the cerebral cortex . . . not in the new brain but in the old." In 1946, he noted that this "high level" of integration was located, not in the frontal lobe as Jackson had suggested, but in the upper end of the brain stem, which Penfield later designated a "centrencephalic system"—a system which includes all those areas of subcortical gray matter (together with their connecting tracts) which serve the purposes of intra- and interhemispheral integration, but from which, he thinks, the corpus striatum should probably be excluded.

The most conjectural aspects of the authors' interpretations relate to their suggestions pertaining to the relationships between cortical, thalamic, and brain stem speech areas. They do convey a convincing notion of preponderantly vertical systems operating in some kind of functional transaction with one another. Each cortical field is likened to a platform for the upward arrival and downward departure of impulses—a platform which permits the sorting out and reorganizing of impulses. Each per-

formance within the cortex seems to be more dependent for functional integrity upon its subcortical relations than upon its cortical connections with neighboring fields. The "cortical detours" provide an "increased allotment of space" to each of several subcortical functional systems.

Neocortical areas yield relatively objective, disinterested, internally perceived experiences, while those relating to the phylogenetically older systems evoke more personalized and self-involved subjective experiences. Thus, the temporal lobe and occasionally the insula may yield, on stimulation, "experiential hallucinations or interpretive illusions." Stimulation of the amygdaloid complex yields psychomotor confusion, which is followed by amnesia. The hippocampus (according to Milner and Penfield) seems to be the repository of neuronal mechanisms that preserve "the stream of consciousness" or, at least, play an important role in the mechanisms of reactivation of such a record of consciousness. It is interesting to note that the commonest evoked *emotional* response is fear, and that there are no reports of evoked pain, taste, or smell.

Speech representation appears to be largely restricted to one hemisphere, usually the left. "If the cases with injury in early life are excluded, there is no difference in incidence of aphasia after operation on the left hemisphere between the left- and right-handed." Even though the patient is left-handed, with weakness of the right hand from his early years, aphasia may follow operation on the left hemisphere. The authors depend initially upon Wada's (1949) sodium amytal test for determining which hemisphere subserves speech.

The last chapter is an interesting departure from the rest of the book and reflects the senior author's abiding concern with the way in which language is initially learned and the instructive implications of this concern as applied to the social problem of teaching supplementary languages expeditiously and effectively.

As compared with previous clinical and physiological observations concerning the central nervous mechanisms relating to speech, the contributions of Penfield and Roberts are monumental. The authors have made their account even more fascinating and moving through their obvious sensitivity to each patient's individuality and welfare and to the ethical problems involved in the physicians' invasion of the patient's brain-mind. This study clearly required a skilled and dedicated team of experts; it is gratifying that they were also thoroughly humane.

ROBERT B. LIVINGSTON
*National Institute of Mental Health* and *National Institute of Neurological Diseases and Blindness*

**Theory of Psychoanalytic Technique.** Menninger Clinic Monograph Series, No. 12. Karl Menninger. Basic Books, New York, 1958. xiii + 206 pp. Illus. + plates. $4.75.

Karl Menninger is an accomplished writer and an experienced psychoanalyst; his book is a most readable didactic presentation of the traditional concepts of psychoanalytic therapy. The author stresses that this is a book on the theory of psychoanalytical treatment, but the assets of the book lie more in his practical recommendations and vivid descriptions of the fundamental psychodynamic phenomena of the treatment—such as regressive transference, countertransference, resistance, and the analyst's interventions. These psychodynamic phenomena are colorfully described, but they are not knit together tightly into a fully convincing theoretical model. As a whole, the author follows the traditional views, although some controversial issues are briefly referred to. The central significance of the transference phenomenon is convincingly stated, and its regressive nature is concretely demonstrated. The author's main emphasis is placed on the frustrating nature of the therapeutic experience which results from the fact that the therapist with his detached, objective, and relatively silent behavior does not satisfy the patient's infantile cravings, which, as the therapy goes on, become more and more infantile. As a result of these frustrations the patient regresses to earlier and earlier modes of feeling and reacting. A schematized regression scale is presented, in which the author follows Sandor Rado's diagram.

The crucial issue of psychoanalytic treatment remains essentially unanswered—namely, why, after a certain period of regression, when a point is reached, the patient turns around and progresses to more adequate forms of organization of his impulses, feelings, and object relations. The author is frank in admitting that his theoretical framework cannot provide a cogent answer to this question. This impasse is the result of his basic scheme, which does not correspond accurately to the actual psychological processes during treatment. Particularly, the fact is overlooked that from the very beginning of treatment, and coincident with the regressive process, continuous, spontaneous, integrative efforts are present which are continuously supported by the therapist's interventions. Regression and integration are simultaneously going on during the whole of the treatment, although the distribution of these processes may differ in the different phases of the treatment.

Perhaps the weakest spot of the theoretical model offered by Menninger is that he does not scrutinize sufficiently the psychodynamic meaning of the term *regression*. A most important, but rather late, contribution of Freud's consisted of discriminating between the two kinds of regression. Originally, by *regression* Freud meant a return to periods of personality organization that have proved satisfactory in the past—a kind of retreat, into a happier past, from difficulties, conflicts, and traumatic experiences which have arisen at some point of mental and physical growth, usually during the early years of family life. Later he introduced another form of "regression"—the return to unsettled traumatic experiences. The simplest examples are dreams in which the dreamer conjures up and reexperiences overwhelming situations of the past. Freud explained this type of regressive phenomena as the ego's effort for subsequent mastery of an unresolved overwhelming experience. This type of return has a definite therapeutic significance. It is the self-curative effort of the "psychic apparatus" to reduce the excessive and never-resolved excitations caused by the traumatic event. Many of the regressive phenomena during psychoanalysis are of this nature, and they have a great therapeutic value. In fact, without them the therapeutic effect of psychoanalysis cannot be explained. Regression in the sense of escape to earlier, relatively satisfactory phases of development can be considered as resistance, and it has anything but a therapeutic value. It may have, however, great research value, giving insight into the earliest modes of feeling, thinking, and behavior.

The other type of regression is highly therapeutic. The patient reexperiences some of his old, unresolved-conflict experiences during treatment, but this reexperiencing takes place under more favorable circumstances. Not only are these revived conflicts of lesser intensity than the original ones but the adult ego is more capable of facing these conflicts, which originally the child's ego could not resolve. Moreover, this reexperiencing of old conflicts takes place in a different framework. In place of the original persons, an objective, helpful, and emotionally uninvolved therapist is now the object of the patient's predetermined reactions. These reaction patterns were responses to the old family situations and do not fit the therapeutic situation. This has a corrective value. This discrepancy challenges the ego, whose basic function is to adjust to a given situation, to find new and more adequate reaction patterns. These are the concepts which readily explain the therapeutic value of the psychoanalytic process.

Menninger gives a very vivid description of the emotional processes which take place during the treatment and also gives an excellent presentation of different types of intervention by the analyst.

Because of his convincing emphasis upon the regressive emotional experiences of the patient, it is somewhat perplexing when the author reconfirms the thesis—which, to be sure, is still shared by a considerable number of analysts—that cognitive insight supported by the interpretations of the therapist is the primary and most specific factor in psychoanalysis. How insight and emotional experiences interact and mutually support or sometimes interfere with each other is probably the least clearly understood and most controversial issue of psychoanalytic theory. Menninger gives a clear picture of both the significance of the emotional experiences and the cognitive processes which take place during treatment, but he gives no thorough evaluation of the interaction between these two basic therapeutic factors.

All in all, the book represents a valiant effort to bring order into the complexity of the psychological processes which take place during a psychoanalytic treatment. It will stimulate the student's urge to understand the principles of what he is doing and discourage the tendency to rely simply on practical rules and regulations. Although he will not receive final or even always correct answers, it will challenge his own thinking and make him try to fill out the gaps.

FRANZ ALEXANDER
*Mount Sinai Hospital,*
*Los Angeles, California*

**Alcohol and the Jews.** A cultural study of drinking and sobriety. Monographs of the Yale Center of Alcohol Studies, No. 1. Charles R. Snyder. Yale Center of Alcohol Studies, New Haven, Conn.; Free Press, Glencoe, Ill., 1958. 226 pp. $5.

Alcoholism is one of the most frequent forms of social pathology. Drunkenness, as a single cause, is responsible for almost half of the total number of arrests of men in our country. It causes incalculable damage to property and a high loss in human lives. No wonder that its causes and effects are the subject of much research and study. Within recent years studies in alcoholism have emphasized three aspects of the phenomenon: the psychiatric (the personality of the alcoholic), the physiological (the constitutional "craving" for alcohol), and the sociological (alcoholism as a symptom of social disorganization).

Snyder, in this stimulating monograph, contributes findings derived from a *cultural* study of drinking among the Jews, who seem to be free, to a marked degree, from the pathological manifestations of alcoholism, despite relatively frequent drinking. These findings are very explicit indeed: "[they] suggest that the emergence of drinking pathologies where drinking is prevalent cannot be explained by exclusive reference to individual psychology or to a mysterious 'craving' for alcohol presumed to be physiologically determined. The possible role of psychophysical processes is not denied but social and cultural phenomena, especially those related to normative or cultural traditions regarding drinking, appear to be essential for the emergence of these pathologies" (page 202).

Snyder's study is based on data collected in a series of interviews with a large number of Jewish men (students and nonstudents) in New Haven, Conn. These data are interpreted in the light of information derived from studies of drinking in non-Jewish groups (Irish Catholics and British Protestants) as well from Jewish traditional (religious) literature pertaining to drinking and other more general sources on Jewish culture. The author's interpretations and conclusions are well illustrated by tables and diagrams. A most helpful and stimulating form of supportive material, which adds a great deal to the value of the monograph, is the use of verbatim quotations from interviews.

The author demonstrates very convincingly the close correlation between Jewish drinking patterns and religious affiliation. Though an orientation toward sobriety is manifest throughout the material, this is found to be strongest among Jews affiliated with the Orthodox group, and it decreases in intensity among the Conservative, Reformed, and "Secular" Jews. The more the Jews become secularized, the more they tend to adopt the drinking patterns—including drunkenness—of the larger society.

The data speak for themselves. However, in my opinion the author attaches too much weight to the significance of the formal affiliation of his respondents with one or another religious group. There are reasons to believe that when Jewish respondents identify themselves with the Orthodox, the Conservative, or the Reformed groups they are actually indicating not so much their adherence to specific religious practices as the degree of their identification with the Jewish culture and its system of values. In other words, the terms *Orthodox, Conservative,* or *Reformed* are frequently used as symbols of cultural identification. Hence, the observed changes in the drinking patterns are in fact associated not with changes in religiosity but with changes in the intensity of cultural identification, which, in turn, are expressed in the movement from the Orthodox to the Reformed congregation.

In order to determine the true significance of the religious element, it would be helpful to view Jewish attitudes toward drinking not only in the light of specific ritual practices but also in conjunction with consideration of other cultural values which are looked upon by Jews as being "Jewish"—values such as a positive attitude toward enjoyment (in moderation) of other good things in life (food and sex), concern with mental and physical health, attitudes toward violence, and so forth.

This suggestion, however, is not intended to detract from the actual merits of Snyder's study. He has proved, in a most satisfactory fashion, the significance of the social science contribution to the understanding of problems in the field of mental health, and his monograph is highly recommended to all those interested in the field of social pathology.

MARK ZBOROWSKI
*Harvard Community Health Project,*
*Harvard School of Public Health*

**Elephants.** A short account of their natural history, evolution, and influence on mankind. Richard Carrington. Basic Books, New York, 1959. 272 pp. Illus. + plates. $5.

To most men elephants are gigantic mammals that may be seen occasionally by going to a zoological park or to a circus, where they can be admired and marveled at because of their huge size and their very obvious intelligence. We are apt to forget, and perhaps many of us are even unaware of the fact, that elephants and men have been closely associated for untold thousands of years, back through human history and prehistory. Indeed, the evolutionary and social history of Man was inextricably interwoven with the history of the elephants and their mastodont cousins throughout the great Pleistocene ice age, and it is only within the past few millenia that Man has emerged as a completely dominant mammal in a world where once the great proboscideans ranged widely and in great numbers across all of the continents.

This book by Richard Carrington will find a welcome niche on the shelves of all who may be interested in elephants and who have not had the opportunity to make first-hand studies of the enormous literature concerning these wonderful animals. Succinctly, and in very readable prose, Carrington sets forth much that is interesting and important about elephants. The reader will find this volume an absorbing account about elephants and a useful reference book for future consultation.

The book is divided into three major sections. The first deals with living elephants—their anatomy, physiology, and ecology; the second, with the long and

highly complex fossil history of the Proboscidea, the great order of mammals of which the modern Asiatic and African elephants are the sole survivors; and the third, with a brief survey of the relationships between elephants and Man. Each of these three sections presents a well-balanced treatment of a very large subject.

In a book such as this it is necessary for the author to condense the material a great deal, and Carrington has handled this difficult task in admirable fashion. It would have been nice if there could have been more illustrations, especially in the first two sections of the book, but considerations of space and economy obviously would not allow this. A good, selected bibliography at the end of the book supplies ample references for the reader who may wish to pursue the subject of elephants beyond this "basic" presentation.

EDWIN H. COLBERT
*American Museum of Natural History* and *Columbia University*

**Handbuch der Physik.** vol. 51. *Astrophysics,* II. Stellar structure. S. Flügge, Ed. Springer, Berlin, 1958. viii + 830 pp. Illus. DM. 175.

Though this book is prosaically subtitled "Stellar structure," it is concerned mainly with the latest theories and hypotheses of stellar evolution. Nothing like it could have been written 10 years ago, and most of its ideas would have been described a generation ago as the outpourings of a group of scientific cranks. I remember vividly an incident at the Yerkes Observatory when a distinguished professor of the University of Chicago—a man well known for his own scholarly research—assured me that it was a waste of time to read an article by A. S. Eddington which purported to show that the central temperature of the sun is 20 million degrees. I also remember an earlier occasion, in 1913, when two leading European astronomers argued that it would be hopeless to attempt to measure the gravitational displacements of star images during an eclipse of the sun because, in the first place, the effect predicted by Einstein probably did not exist, and, in the second place, even if it did, the amount of displacement would be too small to be ascertained.

Lulled by a century devoted to the painstaking accumulation of facts about the universe and the slow interpretation of these facts, we professional astronomers had become (with a few notable exceptions) unduly conservative and cautious in accepting new and revolutionary ideas. We enjoyed the books by Flammarion and Fournier d'Albe but relegated to the domain of belles-lettres their flights of imagination. We recognized Arrhenius as a great chemist but smiled at his fanciful astronomical hypotheses. We failed to comprehend the enormous astronomical significance of cosmic rays, and we neglected to profit by Jansky's epochal discovery of cosmic radioradiation until the radio engineer Grote Reber had learned enough astronomy to show us the way.

All of this conservatism was wiped off the face of the earth in that flash of light which accompanied the first test explosion of the atomic bomb in New Mexico. Today we are no longer surprised when astrophysicists talk about billions of planets belonging to stars other than the sun, or when a radio astronomer seriously considers sending radio signals to a planet revolving around a star of solar type some 10 or 20 light-years away. We accept almost without protest a theory which predicts an internal stellar temperature (in giant stars) of several billion degrees or an average density (in a white dwarf) a million times greater than that of water. And we speculate about the formation of all chemical elements out of hydrogen in stellar interiors and even on the surfaces of many stars.

It may well be that a future historian will criticize us for having lost our balance between judicious conservatism and exuberant revolutionism. He may even paraphrase Martin Gardner's sentences [*Fads and Fallacies in the Name of Science* (Dover, New York, 1957), p. 3] and say: "One curious consequence of the current boom in science is the rise of the promoter of new and strange scientific theories. He is riding into prominence, so to speak, on the coattails of reputable investigators." If it should be true that we are riding on the coattails of our more conservative predecessors, one thing is certain: The ride is the most joyful and exhilarating experience that any scientist has ever had.

In a recent review of volume 50 of this *Handbuch* (*Astrophysik*, I. Sternoberflächen, Doppelsterne), I expressed the opinion that the purpose of an encyclopedia is to present a broad and comprehensive treatment of all fields of a particular discipline and of their interrelations, and that in this respect it should differ significantly from a series of unrelated summarizing articles. I felt that this particular purpose of the encyclopedia had perhaps not been fully achieved in volume 50, even though the quality of the individual contributions could, with very few exceptions be characterized as excellent [see *Z. Astrophys.* **45**, 239 (1958)]. Volume 51 does not elicit this criticism. It is, without doubt, the most important book on general astrophysics that has ever been written, and it can be recommended to astronomers and physicists as the most authoritative account of observational and theoretical astrophysics.

The individual chapter headings are as follows: "Stellar interiors," by Marshal H. Wrubel (in English, pages 1–74); "The Hertzsprung-Russell diagram," by H. C. Arp (in English, pages 75–133); "Stellar evolution," by E. M. Burbidge and G. Burbidge (in English, pages 134–295); "The abundances of the elements in the planets and meteorites," by H. E. Suess and H. C. Urey (in German, pages 296–323); "The abundances of the elements in the sun and stars," by L. H. Aller (in English, pages 324–352); "Variable stars," by P. Ledoux and T. Walraven (in English, pages 353–604); "Stellar stability," by P. Ledoux (in English, pages 605–688); "Magnetic fields of stars," by A. J. Deutsch (in English, pages 689–722); "The theory of white dwarfs," by E. Schatzman (in French, pages 723–751); "The novae," by C. Payne-Gaposchkin (in English, pages 752–765); and "Supernovae," by F. Zwicky (in English, pages 766–785). The volume closes with a subject index in German-English, English-German, and French (the entries in French refer only to the article by Schatzman).

As an observational astrophysicist I was especially interested in the articles by Arp, Aller, Deutsch, and Zwicky, and by Walraven's section on the observational results on variable stars. But the "nucleus" of this volume is probably the magnificent chapter by the Burbidges. The theories of variable stars by Ledoux, of white dwarfs by Schatzman, and of magnetic stars by Deutsch will enable me (and probably many others) to interpret our observations in the light of modern physical theory. I believe that the chapter on "Stellar interiors" is somewhat too short to fully satisfy the reader. Perhaps the author was not given enough space to develop this field adequately.

OTTO STRUVE
*Department of Astronomy, University of California, Berkeley*

**The Fearful Choice.** A debate on nuclear policy conducted by Philip Toynbee, Wayne State University Press, Detroit, Mich., 1959. 112 pp. $2.50.

Philip Toynbee has prepared an interesting debate on nuclear policy by throwing an almost-pacifist challenge to a wide assortment of his high-placed British friends and by collecting and commenting on the essays they sent in reply. He starts by recognizing the great changes that the nuclear scale of destruction has brought about, and most of his correspondents go along with him on that. To the ringing words, "It is inconceivable that the free peoples would sur-

render their liberties without a fight," he replies by describing the modern meaning of "a fight." He believes that there was justification for the last war but that there can be none for the next. The meaning of the word *war* has totally changed. He declares that our weapons are useless before an attack, when to use them would be folly, and that they would be useless after an attack, when to use them would be useless revenge. He fails to recognize at any point the usefulness of our weapons as a deterrent (the weapons exist with the hope that they will never be used but with the determination—this Toynbee considers immoral—that they *shall* be used after an attack, in the belief that such determination is likely to prevent the attack.) He is set straight on this point by Ayer, and when Toynbee concedes superior strength to the Russians, Ayer responds not only with doubt but with the "saturation" argument—that slight "disparity no longer greatly matters."

Toynbee is probably right in considering that the arms race, if it cannot somehow be limited, will almost certainly lead to disaster. However, he considers no half-way measures for ameliorating the situation. He despairs of our mincing diplomacy. What he proposes is unilateral disarmament—by the West if we Americans can be persuaded to go along, or failing that, by a neutral block in Europe, or by Britain alone. He believes that Russia, with the world as its dish, would probably recognize it to be indigestible and would not attempt complete occupation. He considers that occupation after unilateral disarmament is less likely than annihilation is if the arms race continues. He would rather risk occupation than face the race agony of annihilation. Some of his correspondents would rather risk annihilation than face occupation.

Perhaps the most remarkable feature of the debate is the small attention paid to the many-nuclear-nation problem and to the possibility of stopping nuclear tests as a means of controlling the development of nuclear weapons and of tapering off the arms race. One of the most plausible essays is that by Richard Löwenthal, who is prepared to risk "race suicide by accident" rather than accept "slavery by design," because the risk may be deliberately reduced: "We could negotiate steps to stop the spreading of weapons to further powers." In the first half of 1959 there is more reason for optimism concerning the negotiations than there was a year ago when these essays were written.

One often wonders how people react in their thoughts to the nuclear threat, and these essays provide a wide spectrum of interesting answers, ranging from, "Fear is a bad advisor" (Lord Portal of Hungerford) to the Archbishop of Canterbury's, "Sufficient unto the day is the evil thereof," and "the spirit in which we negotiate must be . . . a general readiness to give more than we receive." Toynbee is remarkable in having a father who agrees with him completely; the senior Toynbee comments tersely: "Let us therefore put first things first, and make sure of preserving the human race at whatever the temporary price may be."

This little book is thought-provoking. It is much too brief to give a balanced view of the problem of avoiding thermonuclear war, and too few of the essays are keenly critical of Toynbee's position. None of it is to be swallowed without thorough mastication. It gives an interesting glimpse of America through English eyes. It provides a chance to examine the views of quite a variety of one's fellowmen and, through them, to be stimulated to broaden and strengthen one's own thoughts on the world's most important problem.

DAVID R. INGLIS
*Argonne National Laboratory,*
*Lemont, Illinois*

**The Age of Improvement.** Asa Briggs. Longmans, Green, New York, 1959. xiii + 547 pp. $7.

Certainly any historian faces a major challenge in endeavoring to chronicle and interpret a period of national life in a volume that will be enlightening to the scholar and the general reader alike. In *The Age of Improvement,* a history of England from 1784 to 1867, Asa Briggs has met this challenge most successfully. Recognizing that his chosen period "cuts into what are usually thought of as two contrasting centuries —the age of balance and the age of progress," Briggs explains his choice on the ground that the sense of change felt by all classes of the population gave a unity to these years. According to the author, "it was the 'march' of events which fascinated contemporaries and sometimes horrified them. They were divided about the merits of 'improvement,' but they were at one in admitting that it existed."

The book is truly national in scope. It recounts the events associated with kings and queens, politicians, and military leaders, and it describes the changing lives of the "lower orders"—the farm workers, the mill hands, and the tradesmen. Due attention is paid to the religious, scientific, educational, and labor movements of the period. As one would expect from the author of *Victorian People,* there are sharp characterizations of the leading personalities, from the days of Pitt to those of Disraeli. Besides numerous works of historical scholarship, Briggs has drawn upon much contemporary writing, both serious and popular. He includes many apt quotations in prose and verse.

*The Age of Improvement* is part of a ten-volume history of England being published under the general editorship of W. N. Medlicott, whose own work will carry on the account from 1867 to the present. The excellence of the book by Briggs gives promise that the series will be an outstanding achievement in historical writing.

HIRAM M. STOUT
*Washington, D.C.*

**Colorimetric Methods of Analysis.** Including photometric methods. vol. 2A. Foster Dee Snell and Cornelia T. Snell. Van Nostrand, Princeton, N.J., 1959. $15.

This book is a supplement to volume 2 of the third edition of Snell's *Colorimetric Methods of Analysis* and is primarily a compendium of significant developments in inorganic colorimetry in the 1946 to 1956 period. The authors have adopted the economical plan of periodically publishing supplements instead of continually revising and enlarging volume 2. In addition to colorimetric methods, fluorophotometric, nephelometric, turbidimetric, flame photometric, and ultraviolet spectrophotometric methods are included.

The 68 chapter titles in volume 2A are virtually identical to those in volume 2, and the chapters appear in the same sequence. Each chapter consists of (i) a brief introductory paragraph, (ii) procedures for treating a variety of samples, (iii) cogent discussions and detailed procedures for specific methods, and (iv) miscellaneous methods of limited applicability. Throughout the book the procedures are presented lucidly and concisely. Since the reader is frequently referred to volume 2 for the procedure to be followed in completing the analysis of a specific material or for relevant information, volume 2 should be available for maximum utilization of volume 2A.

In my opinion the methods and procedures presented in volume 2A have not been selected or evaluated critically. In many cases the probable utility and reliability of a specific method is indicated by the space allotted to the discussion. However, the extensiveness of treatment is often proportional to the extent of the original investigation. The reader should also be reminded that the inclusion of a method or procedure in volume 2A does not necessarily indicate superiority to methods and procedures found in volume 2.

It is a Herculean task to keep abreast

of the recent developments pertaining to inorganic colorimetric analysis. The Snells are to be commended for documenting the voluminous recent literature and presenting much useful information in a single volume for practicing analysts. The format and typography of volume 2A are excellent. A complete author index and subject index enhance the value of this book.

DAVID F. BOLTZ
*Department of Chemistry,*
*Wayne State University*

**Grundriss der Allgemeinen Zoologie.** Alfred Kühn. Thieme, Stuttgart, Germany, 1959. vii + 289 pp. Illus. $4.25.

Kühn's *Fundamentals of General Zoology* is one of the best monographs in this field. Published for the first time in 1922, it has become one of the standard works at German universities. Precise formulation, vivid presentation, and exemplary illustrations contribute to the success of the book, which gives the student a systematic introduction to the morphology, physiology, and development of mammalian organisms.

This 13th edition confirms and increases the reputation of the work. Through discussion of modern trends and ideas, it stimulates biological thinking on the part of the reader.

A. T. KREBS
*Radiobiology Division,*
*U.S. Army Medical Research Laboratory,* and *Biology Department,*
*University of Louisville*

**The Stratigraphy of Western Australia.** J. R. H. McWhae, P. E. Playford, A. W. Lindner, B. F. Glenister, and B. E. Balme. Melbourne University Press on behalf of the Geological Society of Australia, 1958 (order from Cambridge University Press, New York). 161 pp. Illus. $8.50.

This useful and informative compendium is expressive of significant advances in the geology of western Australia. Not only does it document wide, first-hand stratigraphic and paleontologic experience in western Australia on the part of the writers and their colleagues, but it effectively summarizes pertinent information drawn from 188 published papers and 50 unpublished reports, including those of oil companies. References to the literature are well documented.

The reader is impressed with the account given of the impact of Australian exploration for petroleum, which immeasurably stimulated geological progress in a vast and, until quite recently, little known territory. Stratigraphy is recognized as being technologically basic in this search, and, at the same time, indispensable from the academic standpoint in connection with structural and historical interpretation. Due credit is given the geologists of the "West Australian Petroleum Pty., Ltd." (WAPET) and of the Bureau of Mineral Resources.

Two-thirds of western Australia is shown to be Precambrian. The remaining area falls in seven somewhat arbitrarily defined structural basins wherein the strata range in age from Cambrian to Tertiary. In a counterclockwise direction from northeast to southeast around the continental periphery these basins are as follows: (i) Bonaparte Gulf, (ii) Ord, (iii) Fitzroy, (iv) Canning, (v) Carnarvon, (vi) Perth, and (vii) Eucla. Older Paleozoic strata are best exposed to the north in the Ord, Bonaparte Gulf, and Fitzroy basins. In the Canning basin Jurassic beds predominate, while in the Carnarvon and Perth basins Permian, Jurassic, and Cretaceous sediments are well exposed. Tertiary rocks prevail at the surface in the Eucla basin on the south.

The generalized geologic map, drawn to a scale of 1 inch to 80 miles, shows only undifferentiated rock systems. A few major fault zones and other structural trends are also shown. Certain anticlines and positions of WAPET drill holes are plotted. The fact that very large areas are shown without geologic detail cannot fail to give the impression that much geological exploration remains to be done.

Stratigraphic descriptions of each system and of its formational units are given in order, beginning with the Cambrian. Under each system the units in each of the seven basins are considered separately. Six page-size paleogeographic maps and nine correlation charts are presented in conjunction with the stratigraphic descriptions of each geologic system.

Of special interest are the widespread plateau basalts beneath the Middle Cambrian formations. Only recently have Silurian and Ordovician rocks been recognized in western Australia and described. The Devonian and its faunas, however, have become fairly well known in the Carnarvon and Fitzroy basins, where reef complexes are recognized.

Permian rocks are shown to be thicker and more widespread in western Australia than in any other section of the continent. The Permian was the main coal-forming period and is of special interest historically because of the widespread occurrence of tillites.

Jurassic deposits are mainly continental, though there are thin marine beds. Deposition appears to have been continuous from the Upper Jurassic to the Lower Cretaceous.

Cretaceous rocks are extensive in all the basins except Bonaparte Gulf and Ord. In the Carnarvon basin the Lower Cretaceous Birdrong formation is of great importance as an aquifer and is locally an oil reservoir.

C. W. MERRIAM
*Paleontology and Stratigraphy Branch,*
*U.S. Geological Survey,*
*Menlo Park, California*

## New Books

*Approximate Methods of Higher Analysis.* L. V. Kantorovich and V. I. Krylov. Translated by Curtis D. Benster. Interscience, New York, 1958. 696 pp. $17.

*Behavior of Enzyme Systems.* An analysis of kinetic and mechanism. John M. Reiner. Burgess, Minneapolis, Minn., 1959. 329 pp.

*A Course of Pure Mathematics.* G. H. Hardy. Cambridge Univ. Press, New York, ed. 10, 1959. 521 pp. Paper, $3.75.

*Electrons, Elements and Compounds.* Eric Hutchinson. Saunders, Philadelphia, 1959. 565 pp.

*Elements of Modern Mathematics.* Kenneth O. May. Addison-Wesley, Reading, Mass., 1959. 623 pp. $6.50.

*Elements of Wave Mechanics.* N. F. Mott. Cambridge Univ. Press, New York, 1958. 156 pp. Paper, $2.95 (student edition).

*How to Help Your Children.* The parents' handbook. Advice from William C. Menninger, Ashley Montagu, Paul Witty, and others. Sterling, New York 16, 1959. 640 pp. $4.95.

*Introductory Calculus.* Donald E. Richmond. Addison-Wesley, Reading, Mass., 1959. 222 pp. $5.50.

*La Mesure Précise du Temps.* En fonction des exigences de la science. B. Decaux. Masson, Paris, 1959. 126 pp. Paper, F. 1300.

*Progress in Biochemistry.* A report on biochemical problems and on biochemical research since 1949. Felix Haurowitz. Interscience, New York; Karger, Basel, Switzerland, 1959. 369 pp. $8.50.

*Protides of the Biological Fluids.* Proceedings of the sixth colloquium, Bruges, Belgium, 1958. H. Peeters, Ed. Elsevier, Amsterdam, Netherlands, 1959 (order from Van Nostrand, Princeton, N.J.). 339 pp. $8.50.

*A Short Introduction to Anatomy. (Isagogae Breves).* Jacopo Berengario da Carpi. Translated with an introduction and historical note by L. R. Lind; anatomical notes by Paul G. Roofe. Univ. of Chicago Press, Chicago, 1959. 239 pp. $5.

*Silicones.* R. N. Meals and F. M. Lewis. Reinhold, New York; Chapman & Hall, London, 1959. 278 pp. $5.95.

*Strategy and Market Structure.* Competition, oligopoly, and the theory of games. Martin Shubik. Wiley, New York; Chapman & Hall, London, 1959. 405 pp. $8.

*The Structure and Function of Subcellular Components.* Biochemical Soc. Symp. No. 16. E. M. Crook. Cambridge Univ. Press, New York, 1959. 100 pp. $4.25.

# Reports

## Intellectual Level Measured by Army Classification Battery and Serum Uric Acid Concentration

*Abstract*. In a group of 817 individuals inducted into the U.S. Army, serum uric acid concentration was measured. The values were compared with scores secured on intelligence tests used at the Army reception center. A significant but low level of positive correlation between the two sets of values was found.

Students of arthritis have from time to time recorded the impression that the number of prominent and successful people suffering from gout is remarkably high, considering the relative rarity of the disease. In a recent review of a segment of the history of gout (*1*), one of us (D.S.) collected an impressive list of names of persons prominent in science, letters, diplomacy, and war who purportedly had gout. On more than one occasion it has been suggested that a causal relationship between gout and some measure of human achievement may exist.

It is possible that successful people have a tendency to ingest a diet richer in protein and purine than is usual. Such a diet might result in hyperuricemia and, in the predisposed individual, could ultimately lead to gout. On the other hand, an alternative causal relationship might be that some phase of the metabolic defect in gout, possibly the hyperuricemia, produces enhanced activity of the cerebral cortex. The latter mechanism is perhaps inherent in a suggestion by Orowan (*2*), who proposes that the remarkable development of the human cerebrum stems from the mutation, occurring early in anthropoid phylogeny, which resulted in the loss of hepatic uricase. The consequent elevation in blood uric acid concentration is pictured as stimulating the cerebral cortex, a claim for which no documentation is supplied.

In an answering note (*3*), Haldane points out, among other things, that the postulate of Orowan would imply a correlation between intelligence and the level of blood uric acid concentration. Such a correlation, he states, has not been noted.

The purpose of the present communication is to report the quest for such a correlation. A total of 817 Reserve Forces Act (1955) trainees from the reception station at Fort Dix, N.J., were studied (*4*). The score achieved by each inductee in the Army Classification Battery (ACB) was recorded. This collection of tests (*5*) is designed to measure intelligence and certain special aptitudes and correlates well with other measures of intelligence. A sample of blood serum from the routinely collected blood specimen was also secured from each subject. At the time of collection of the blood, the inductees, all young adult males, had been on the station and on a fairly uniform diet for about 48 hours.

The sera were analyzed for uric acid by a uricase method (*6*) involving measurement of optical density at the maximum of absorption for uric acid, 292 mμ. The mean value for uric acid in this population group was 5.06 mg per 100 milliliters, with a range from 1.05 to 8.74 mg and a standard error of 0.033. The mean value for the ACB test scores was 118.1, with a range from 50 to 156 and a standard error of 0.70.

The coefficient of product-moment correlation, determined by the formula

$$r = \frac{N\Sigma XY - \Sigma X\Sigma Y}{\sqrt{[N\Sigma X^2 - (\Sigma X)^2][N\Sigma Y^2 - (\Sigma Y)^2]}}$$

was found to be + 0.0759. The hypothesis that the observed value of $r$ arose from an uncorrelated normal population was tested (7, p. 343) by setting

$$t = r\sqrt{(N-2)/(1-r^2)}$$

and referring to the $t$-distribution for $N$-2 degrees of freedom (*8*). The value of $t$ was 2.17. Thus, the probability of obtaining an $r$-value equal to or exceeding in absolute value that observed is approximately 0.03 and the probability of obtaining a *positive* $r$ equal to or exceeding that observed is approximately 0.015.

The Spearman coefficient of rank correlation provides a test for correlation which does not involve the assumption of normal distribution. It was determined by the formula

$$\rho = 1 - \frac{6\Sigma D^2}{N(N^2-1)}$$

ties being cared for by the bracket rank rule (*9*). The value of $\rho$ was found to be + 0.0742. For sufficiently large $N$ (*7*), the significance of $\rho$ may be tested in Student's distribution by putting

$$t = \rho\sqrt{(N-2)/(1-\rho^2)}$$

The value of $t$ was 2.20, and the probability of obtaining such a positive $\rho$, or greater, by random sampling from an uncorrelated population is approximately 0.015, in close agreement with the result when $r$ is used.

From these findings it may be concluded that a low level of positive correlation, significant to 1.5 percent, does indeed exist between the score attained in the ACB test and the level of uric acid in blood serum in the population studied. Clearly, the present data provide no basis for discrimination among the several possible causalities for such a correlation.

DEWITT STETTEN, JR.
JOHN Z. HEARON
*National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland*

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4. We wish to acknowledge the cooperation of Maj. R. W. Sherwood, Maj. C. E. Motson, Maj. C. A. Horan, M/Sgt. E Patterson, Sfc. W. Tierney, and Sgt. J. P. Cruz, and of their staffs, all of the Fort Dix Health Center. We are also indebted to Lt. Col. W. R. Wilkin of Walter Reed Hospital for information about the psychological testing program of the U.S. Army and to J. E. Lieberman and Dr. J. E. Seegmiller of the National Institutes of Health for assistance in special phases of this problem. This study was made with the technical assistance of Louise R. Miller, Dolores L. Lowery, and Dorothy Lathrop.
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16 February 1959

*Instructions for preparing reports.* Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* 125, 16 (1957)].

## Effect of pH on Biological Activity of Chorionic Gonadotropin

*Abstract.* Increasing the *p*H from 3.0 to 10.8 increased the uterine weight threefold and the number of positive vaginal smears from 0 to 78 percent in immature rats injected with chorionic gonadotropin in aqueous solution. Activity of a solution held at *p*H 2.6 and 5°C for 24 hours was restored by neutralization.

Recently this laboratory received for assay a commercial sample of chorionic gonadotropin which consisted of a vial containing the dry chorionic gonadotropin powder and a second vial containing an aqueous diluent in which was incorporated, among other things, 25 mg of thiamine hydrochloride per milliliter. In accordance with the usual practice, the powder was first dissolved in the diluent and was then further diluted with 10-percent alcohol in order to obtain the proper dosage range for the bioassay. For comparison, similar solutions of International Standard chorionic gonadotropin in 10-percent alcohol only were prepared. The sample failed to elicit a uterine weight response when injected into immature female rats in total doses of 0.3 and 0.6 international unit per rat, whereas the International Standard chorionic gonadotropin at these doses showed the activity expected. The injections were made subcutaneously in two equal daily injections for 3 days, with sacrifice of the animals on the 5th day.

The assay was repeated, but the sample diluent was omitted and the sample powder was dissolved directly in 10-percent alcohol. The powder now showed the full labeled potency.

When the International Standard chorionic gonadotropin was dissolved in the sample diluent or in 10-percent ethyl alcohol containing an equivalent amount of U.S.P. thiamine hydrochloride, the International Standard chorionic gonadotropin showed no activity at the usual doses administered. However, when a solution of the International Standard chorionic gonadotropin was injected at one site and the thiamine hydrochloride was injected at another site simultaneously, there was no inhibition of activity.

Since it has been reported that acid solutions of chorionic gonadotropin are unstable (*1*), International Standard chorionic gonadotropin in 10-percent alcohol containing hydrochloric acid equivalent to that supplied by the thiamine hydrochloride (*p*H 2.6) was injected, and there was no response. However, when the solution of chorionic gonadotropin so prepared was neutralized with NaOH after standing at 5°C for 24 hours, full activity was restored; this indicated that stability was not a factor.

Table 1 shows the results of two experiments in which the *p*H was varied from 3.9 to 10.8. In these experiments all vaginas were opened with a cotton swab on the evening of the 4th day and vaginal smears were made on the 5th day at 96 and 100 hours after the first injection; following this the animals were sacrificed and their uteri were weighed. In the first experiment the *p*H of the injection medium was varied by the addition of either dilute HCl or dilute NaOH, the final volume of each group being kept constant. In the second experiment the *p*H was adjusted by means of McIlvaine's phosphate-citric acid buffer (*2*), and with dilute NaOH.

As Table 1 demonstrates, not only is the activity of chorionic gonadotropin inhibited at a low *p*H but it is considerably enhanced at a high *p*H. These observations are important in connection with the development of an official method of bioassay for this drug. It is also of interest to know whether the effects noted here also obtain when the drug is used in human beings.

Recently Banik and Chakravarti (*3*) reported that the activity of human chorionic gonadotropin was inhibited when injected in the male toad in the same solution with quinine dihydrochloride, ergotoxine, ethanesulfonate, emetine hydrochloride, or atropine sulfate. It is possible that the inhibition noted was due to the low *p*H of the injected solutions rather than to an inhibitory action of the drugs themselves.

ERNEST J. UMBERGER
GEORGE H. GASS
*Bureau of Biological and Physical Sciences, Food and Drug Administration, Washington, D.C.*

Table 1. Effect of the *p*H of the injection medium on responses of immature rats to 0.6 units of International Standard chorionic gonadotropin.

| *p*H | Buffer | Uterine weight (mean ± standard error) | Vaginal smear | | |
|---|---|---|---|---|---|
| | | | Positive (No.) | Animals (No.) | Positive (%) |
| | | *Experiment A* | | | |
| 3.2 | HCl | 39.5 ± 4.5 | 0 | 11 | 0 |
| 6.0 | None | 60.2 ± 6.8 | 3 | 12 | 25 |
| 8.6 | NaOH | 71.5 ± 9.8 | 8 | 13 | 62 |
| 10.8 | NaOH | 98.6 ± 9.1 | 10 | 13 | 77 |
| Control | None | 42.0 ± 3.6 | 0 | 12 | 0 |
| | | *Experiment B* | | | |
| 3.0 | Phosphate-citric acid | 33.5 ± 8.5 | 0 | 18 | 0 |
| 5.0 | Phosphate-citric acid | 49.2 ± 6.5 | 2 | 18 | 11 |
| 7.0 | Phosphate-citric acid | 73.4 ± 6.7 | 6 | 18 | 33 |
| 9.6 | NaOH | 78.1 ± 4.9 | 9 | 18 | 50 |
| 10.8 | NaOH | 109.2 ± 6.1 | 14 | 18 | 78 |

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17 February 1959

## Male Sterility Induced in Tomato by Sodium 2,3-Dichloroisobutyrate

*Abstract.* Spraying tomatoes with 0.3 percent sodium 2,3-dichloroisobutyrate (FW-450) at anthesis induced male sterility for 12 days, beginning 12 days after treatment. Only 20 percent fewer fruits were set on treated plants hand-pollinated with pollen from unsprayed plants than were set on untreated plants. The flowers again showed normal fertility 37 days after treatment.

The high cost of $F_1$ hybrid tomato seed has been one of the factors limiting commercial use of such seed. The use of male sterile mutants to eliminate the necessity for hand emasculation has been suggested as a means of reducing the cost of hybrid seed. Larson and Paur (*1*) described a functional male sterile mutant and suggested techniques of utilizing it. Many male sterile mutants have been identified, and some were listed by Rick (*2*). Before it would be possible to produce hybrid tomato seed commercially by means of these techniques, a breeding program of undetermined duration would probably be necessary, unless suitable male sterile mutants could be found by searching in large field populations, where, according to Rick (*3*), the normal incidence is about 0.05 percent. Alternatively, male sterility might be induced in one of the parents by irradiation, as discussed by Lesley and Lesley (*4*). If male sterility could be induced in tomatoes by means of a chemical, $F_1$ hybrid seed could be produced without hand emasculation and without

the delay required for breeding programs, and produced cheaply, as shown by Hafen and Stevenson (*5*), who reported a pollination cost of about $6 per pound of seed where male sterile mutants were used.

A selective gametocide, sodium 2,3-dichloroisobutyrate (*6*), induced male sterility in cotton, according to Eaton (*7*). The gametocide was tested on field tomatoes at Morden, Manitoba, Canada, in 1958. The varieties Early Chatham, Earlinorth, Monarch, Mustang, Cavalier, Early Lethbridge, Early Hybrid, Manitoba, Bounty, Scotia, and Harrow were used. Spray treatments consisted of applications of four concentrations (0.075, 0.15, 0.3, and 0.6 percent) of the chemical in water; each concentration was applied on three different dates (23 June and 11 and 29 July). There were two unsprayed controls. Each spray was applied to a single row which consisted of 55 plants, five plants of each of the 11 varieties. The tractor-mounted sprayer was operated at a pressure of 45 lb/in.$^2$ to give an application rate of 80 gal/acre over the area actually sprayed. When first sprayed, the plants had an average spread of 16 in. and a height of 10 in.; at the second spraying they had a spread of 22 in. and a height of 13 in.; they were not sprayed to the point of run-off on either occasion.

The fertility of the blossoms was evaluated in weekly fruit counts. Figure 1 presents the results for the treatments of 23 June, when the first flowers were at anthesis. The curves represent the average number of fruits set per plant for the 11 varieties.

In the 14-day period between 21 and 35 days after treatment, the number of fruits set on the unsprayed controls averaged 9.8 per plant, in comparison with 10.0, 2.9, 0.9, and 0.2 fruits for the plants sprayed with the 0.075-, 0.15-, 0.3-, and 0.6-percent concentrations, respectively, of the gametocide. The 0.075-percent concentration did not induce sterility. The 0.15 percent concentration caused some reduction in fruit set, and the 0.3 and 0.6 percent concentrations almost prevented further set. In the following 7-day period, between 35 and 42 days after treatment, fruit set was 30.6 for the controls and 33.6, 25.8, 10.7, and 0.8 for the plants treated with the 0.075-, 0.15-, 0.3-, and 0.6-percent concentrations, respectively, of the gametocide. In this period the two low concentrations had little effect, the 0.3 percent concentration had an intermediate effect, and the 0.6 percent concentration practically prevented set. The finding of 1.0 fruit set in the 3-week period for plants treated with the 0.6-percent concentration of the gametocide was attributed to pretreatment fertilization and delayed expansion of the fruit. About 6

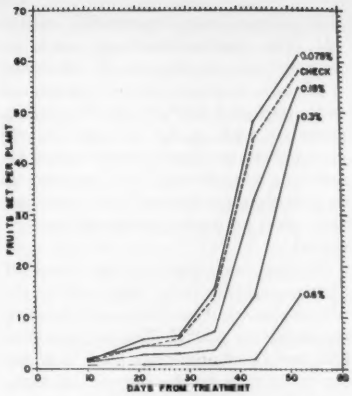


Fig. 1. Average number of fruits set per plant for 11 varieties of tomato sprayed 23 June with 2,3-dichloroisobutyrate in four concentrations (solid lines) compared with average number for unsprayed controls (dashed line).

days after anthesis, fruits were sufficiently expanded to be identified as pollinated and therefore to be counted as set.

The second application of the gametocide was made 11 July, when about four fruits were set per plant (see Fig. 2). In the 17-day period between 17 and 34 days after treatment, fruit set was 44.0 fruits per plant for the controls and 28.9, 21.9, 5.9, and 2.6 fruits for plants treated with the 0.075-, 0.15-, 0.3-, and 0.6-percent concentrations, respectively, of the gametocide. The rate of fruit set was substantially reduced by treatment with the 0.3-percent gametocide, and set was almost inhibited by treatment with the 0.6-percent concentration. In the following 7-day period only 2.3 fruits were set

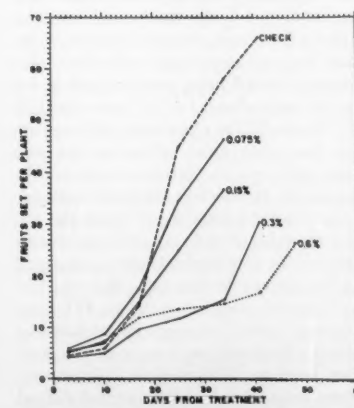


Fig. 2. Average number of fruits set per plant for 11 varieties of tomato sprayed 11 July wtih 2,3-dichloroisobutyrate in four concentrations compared with average number for unsprayed controls.

on the plants that had been sprayed with the 0.6-percent concentration; however, 14.9 fruits were set on these treated with the 0.3-percent concentration—a finding that indicated return to fertility.

Gametocide applications made on 29 July (for which data are not presented) to plants with an average set of 16 fruits produced a pattern of fruit set similar to that for the two earlier treatments. In all three instances application of a 0.6-percent concentration of the gametocide caused foliage to yellow within several days, reduced the growth rate, and inhibited the production of pollen almost immediately.

The male fertility of treated plants was further evaluated by recording the presence or absence of pollen and by testing the viability of any pollen produced by applying it to emasculated flowers of unsprayed plants. The female fertility of treated plants was evaluated by pollinating the flowers with normal viable pollen obtained from unsprayed plants of the same variety. It was found that male sterile flowers could be identified by the lighter yellow color of the staminal tube. Results of this part of the experiment for the 23 June and 11 July applications showed no male or female sterility attributable to treatment with the 0.075-percent concentrations. The 0.15-percent concentration induced a high degree of male sterility for about 13 days, beginning 15 days after treatment, but complete absence of pollen was not observed to result from treatment at this concentration. A slight reduction in female fertility was apparent. The 0.3-percent concentration caused complete absence of pollen for about 12 days, beginning 12 days after treatment. During this period, about 30 percent of the flowers on plants sprayed with the 0.3 percent concentration, when pollinated with normal pollen, set fruit, as compared with about 50 percent of the flowers on unsprayed control plants; this finding was interpreted as indicating reduced female fertility in the treated plants. The return to normal pollen production was gradual. By 37 days after treatment, pollen production was normal. The 0.6 percent concentration induced complete male sterility (absence of pollen) for a period of about 19 days, beginning 12 days after application. Pollen production was normal 37 days after treatment. No fruits were set when normal pollen was applied between 15 and 22 days after treatment to the flowers of plants treated with this 0.6-percent concentration; this was taken to indicate female sterility. Female fertility was again normal 37 days after treatment.

The 11 varieties of tomato tested did not differ in their response to the gametocide with respect to fruit setting. The

variety Early Lethbridge showed slightly more yellowing of foliage than the others, and the reduction in rate of growth was slightly greater in this variety.

JOHN F. MOORE
*Agricultural Research Department,*
*Campbell Soup Company,*
*Riverton, New Jersey*

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12 January 1959

## Ionizing Energy as an Aid in Exchange Tritium Labeling

*Abstract.* The tritium labeling of organic compounds by the Wilzbach technique—that is, by simple exposure of the compound to tritium gas—is greatly accelerated by the simultaneous exposure of the system to a silent electrical discharge. The incorporation of tritium into benzene was increased by a factor of about $10^4$ without undue decomposition. Cobalt-60 γ-rays were found to be far less useful for increasing the tritium incorporation.

The method described by Wilzbach (*1*) for the labeling of organic compounds by exposure to tritium gas has come into wide use. The compound to be labeled is exposed to subatmospheric pressures of tritium gas at room temperature for a few days. The radioactive gas is then removed, and the exposed compound is rigorously purified by recrystallization, distillation, or chromatography. By this technique, labeled organic compounds with specific activities of the order of 10 mc/g may be obtained.

It has been shown that reactions with recoiling tritons from the labeling gas are not the principal process by which the organic substrate becomes labeled (*2*). The most likely process appears to be reactions between ionized or excited organic molecules and the tritium gas, a supposition furthered by the work of Ahrens *et al.* (*3*), in which was measured the product distribution obtained by exposing hydrocarbons to tritium-labeled hydrogen and to γ-radiation. It therefore seemed to us that the exchange labeling could be greatly speeded up by providing the system with an external source of ionizing energy. For this purpose we applied, separately, a silent electrical discharge and γ-rays from a $Co^{60}$ source to a benzene-HT system (*4*). The electrical-discharge work recalls a recent publication by Wolfgang *et al.* (*5*), in which organic compounds were irradiated with $T^+$ and $T^+_2$ ions accelerated with a d-c voltage. In our experiments we used a high-voltage alternating current whose sole purpose was to provide a greater number of excited molecules; no ion accelerations were involved.

Tritium was kept in the form of uranium tritide, $UT_3$, from which the tritium gas could be obtained by heating the tritide to 450°C. The vacuum line and associated apparatus used to transfer the tritium to the organic substrate were similar to those recently described in *Nucleonics* (*6*).

The effect of the silent electrical discharge was determined in the following way: Benzene (600 μl) was exposed to 40 mc of tritium (partial pressure of $H_2 + HT$, 210 mm) in the apparatus shown in Fig. 1. The volume of the space occupied by the benzene vapor was about 60 $cm^3$; therefore, only 4 percent of the benzene was in vapor form and the remainder was in liquid form at the bottom of the tube. A silent discharge (alternating current, 20 kv, 1 ma) was passed through the system for 1 hour. The hydrogen-tritium gas was removed, and the irradiated benzene sample was purified to constant specific activity by vapor-phase chromatography. Two passes through a 5-ft paraffin column were enough to accomplish this; further passes through paraffin, Silicone, Carbowax, or Ucon columns led to no change in the specific activity. After the paraffin-column purification, 0.67 mc was found to have been incorporated into 500 μl of the purified benzene. Very little decomposition of the benzene was evident in this experiment. The isotopic percentage of the tritium used was only 0.1, and under these conditions the Wilzbach technique alone (that is, without the accompanying electrical discharge) would have given a total activity of only about $4 \times 10^{-5}$ mc (or 0.04 μc) in the 500 μl of benzene. It is apparent that, with more tritium in the gas, very high specific activities can be obtained by the electric discharge method.

In a second experiment (with the entire assembly in a horizontal position to spread out the liquid benzene) passage of the current for 5 hours (46.5 mc, 256 mm partial pressure of the $H_2$-HT gas) resulted in the incorporation of 5.56 mc into a 200-μl aliquot portion of the purified benzene. However, in this experiment only 200 μl of the original 600 μl of the benzene was recovered. Extensive decomposition (roughly 50 percent) was observed to have taken place. Consequently, the conditions of the first experiment, with a shorter time of exposure to the electric discharge, are to be recommended.

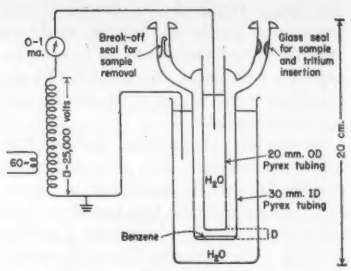


Fig. 1. Electrical discharge apparatus.

Further experiments were performed to test whether a change in the distance *D* (Fig. 1) through the liquid benzene would alter the amount of radioactivity incorporated under conditions otherwise identical. No significant differences were observed between an experiment performed with $D = 5$ mm and another with $D = 25$ mm.

To determine the effect of γ-radiation on the incorporation of tritium into benzene, the following experiment was performed: In each of two similar glass vessels (40-ml volume) were placed 600 μl of benzene and a mixture of $H_2$ and HT (specific activity 2.014 mc/$cm^3$ at standard temperature and pressure; total activity 25 mc). The total pressure in each vessel was 330 mm (benzene, 80 mm; $H_2$-HT, 250 mm). The vessels were then glass-sealed. One vessel was allowed to stand for 24 hours at room temperature. The total energy expended in this vessel by the tritium was $4.7 \times 10^{17}$ ev, and the energy absorbed by the gases would be almost equal to this amount (*7*). The other vessel was irradiated for 24 hours at room temperature with γ-rays from a $Co^{60}$ source. The total dose delivered to the gases was $2.7 \times 10^{19}$ ev. The vessels were then opened, through break-off seals, on a vacuum line. The hydrogen-tritium gas was removed, and the irradiated benzene samples were purified to constant specific activity by vapor-phase chromatography. In the "control" benzene a total of 0.565 μc was incorporated; in the γ-irradiated sample a total of 3.85 μc was incorporated. The tritium labeling in the irradiated sample was therefore greater by a factor of 6.8.

A second experiment was performed in exactly the same way as the first except that in both vessels the partial pressure of the $H_2$-HT was 70 instead of 250 mm, and the total activity was 7 instead of 25 mc. As before, the partial pressure of the benzene was 80 mm. The total energy expended in (and absorbed by) the control vessel was $1.3 \times 10^{17}$ ev. The gases in the γ-irradiated vessel received

an additional $2.7 \times 10^{19}$ ev. The total incorporations obtained were 0.16 μc for the control and 1.11 μc for the γ-irradiated sample; thus, the incorporation was increased by a factor of 6.9. This factor is similar to that found in the previous experiment, and the total activities incorporated in the two experiments are, therefore, proportional to the HT concentrations.

These experiments indicate that the γ-radiation does, as expected, increase the rate of tritium labeling. However, the factor of increased labeling (6.8 or 6.9) is much lower than the increase in energy delivered to the system (57 in one case, 207 in the other). Consequently, it appears that the increased labeling is obtained only at the expense of molecular destruction—that is, the γ-radiation increases the ratio of destruction to labeling. It is thus inferior to exposure to higher tritium specific activities as a means of increasing the amount of labeling for a given exposure time.

RICHARD M. LEMMON
BERT M. TOLBERT*
WALTER STROHMEIER†
IRVILLE M. WHITTEMORE
*Lawrence Radiation Laboratory,*
*University of California, Berkeley*

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* Present address: Department of Chemistry, University of Colorado, Boulder.
† Appointment supported by the International Cooperation Administration under a program administered by the National Academy of Sciences. Present address: Institut für Physikalische Chemie, Universität Würzburg, Würzburg, Germany.

15 April 1959

## Bilirubin Inhibition of Heme Biosynthesis

*Abstract.* The conversion of protoporphyrin and iron to heme is catalyzed by a soluble enzyme prepared from rat liver. This reaction is inhibited by bilirubin, and initial kinetic studies suggest that the inhibition is due in part to a competition between protoporphyrin and the bile pigment. Implications of this finding in hyperbilirubinemia are mentioned.

Hyperbilirubinemia, a condition in which the blood concentration of unconjugated (indirect) bilirubin is markedly increased, is a frequent clinical problem in the newborn infant. In these cases hyperbilirubinemia may be accompanied by serious brain injury. Since brain tissues are very sensitive to even mild states of anoxia, any interference with their ability to carry out biological oxidation might result in cellular damage. Bilirubin has already been implicated experimentally in this way through its inhibition of aerobic oxidation and uncoupling of phosphorylation in both brain and liver tissue (*1*). A more specific, but perhaps related, biochemical effect of bilirubin is described in this report (*2*).

In this laboratory we have been studying the mechanism of the reaction by which iron and protoporphyrin combine to form heme (*3*). The reaction is the last step in heme biosynthesis and is catalyzed by a soluble enzyme found in such varied tissues as rat and chick embryo liver, beef heart, chicken erythrocytes, and rat brain. On comparing the structure of one of the substrates, protoporphyrin, with bilirubin it can be seen that they are both tetrapyrroles with identical side chains and that they can exist in spatially similar arrangements. The work of Granick and Gilder (*4*) with *Hemophilus influenzae* has shown that the propionate groups of protoporphyrin attach to the apoenzyme and that the vinyl groups are essential for iron incorporation. This being the case, it is not difficult to visualize how bilirubin could act as a competitive inhibitor of protoporphyrin utilization, since reduction of the γ-methene bridge between the pyrroles bearing the propionate groups would allow restricted rotation but still have little effect on their relative spatial positions, whereas complete removal of the α-methene bridge could so affect the spatial arrangement of the vinyl groups that they would be nonfunctional.

In order to test this hypothesis we used the soluble enzyme preparation obtained from rat-liver mitochondria and both the isotopic and spectrophotometric assays reported previously (*3*). Only one change was made in these procedures—the reaction was stopped after only 20 minutes' incubation to assure that measurements were made at a constant reaction rate. Bilirubin (*5*) was dissolved in 10-percent sodium carbonate, adjusted to *p*H 8 with HCl, and diluted to a concentration of 0.007*M*.

As is shown in Fig. 1, bilirubin inhibited simultaneously the utilization of protoporphyrin and the uptake of iron-59, the latter to a slightly greater extent. Even though the enzyme was in a crude form, preliminary kinetic studies were carried out in an effort to learn whether bilirubin was inhibiting primarily through competition with protoporphyrin. By varying the concentrations of these two compounds and keeping iron

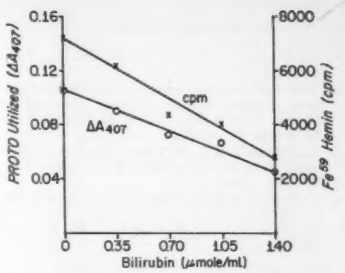


Fig. 1. Effects of bilirubin on heme biosynthesis as measured simultaneously by protoporphyrin utilization and by iron-59 incorporation.

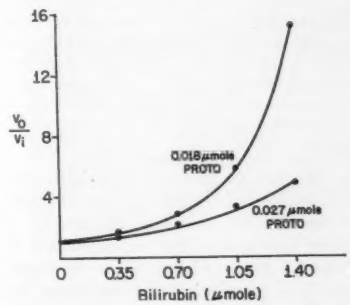


Fig. 2. Kinetics of bilirubin inhibition at different protoporphyrin concentrations.

constant, the data plotted in Fig. 2 were obtained. These data suggest competitive inhibition, since the curves for different substrate (protoporphyrin) concentrations are in the proper relation and intersect the ordinate at unity. However, the curves are not straight lines but increase approximately logarithmically with increasing inhibitor concentration. Thus, there may be competitive inhibition with protoprophyrin with a second effect superimposed, perhaps involving the iron directly. As an inhibitor of this reaction bilirubin is quite active, since 50-percent inhibition is obtained with a bilirubin concentration of $10^{-3}M$ and a bilirubin-protoprophyrin molar ratio of 53.

In conclusion, it should be mentioned that bilirubin inhibits this same reaction in rat-brain homogenate. While the data presented briefly here do not explain the varied clinical manifestations of hyperbilirubinemia, they do show that one action of bilirubin in this disease may be inhibition of the biosynthesis of heme, the prosthetic group of numerous enzymes essential for biological oxidation.

ROBERT F. LABBE
MERLIN R. ZASKE
ROBERT A. ALDRICH
*Department of Pediatrics,*
*School of Medicine,*
*University of Washington, Seattle*

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2 February 1959


## Stratospheric Fallout of Strontium-89 and Barium-140


*Abstract*. A series of nuclear test explosions which occurred in the fall of 1958 caused a very large increase of $Sr^{89}$ and $Ba^{140}$ in the stratosphere. The $Ba^{140}/Sr^{89}$ ratio in the stratosphere, and hence in the troposphere, has decreased steadily since then with a half-life of approximately 17 days.


The last nuclear test explosion seems to have occurred sometime in early November 1958, and it appears as if there will be no more test explosions, at least for the time being. Since the fission products remain in the troposphere for only a month or two, the fallout since December or January must have originated almost exclusively from the stratosphere. In other words, we are now dealing with a "pure" stratospheric fallout, and the period of suspension of nuclear tests provides an excellent opportunity to study the mechanism of the stratospheric fallout.

Samples of rain and snow were collected on the roof of the chemistry building of the University of Arkansas, and the $Sr^{89}$ and $Ba^{140}$ contents were determined radiochemically by a method described earlier (*1*).

Three pancake-type counters (Anton 1007TA) surrounded by cosmic ray counters, and placed within an iron shield, were used for the radioactivity measurements. The backgrounds of the counters were 1.7, 2.0, and 1.8 count/min, respectively, in anticoincidence with the surrounding cosmic ray counters. The experimental results obtained are shown in Table 1 and Fig. 1.

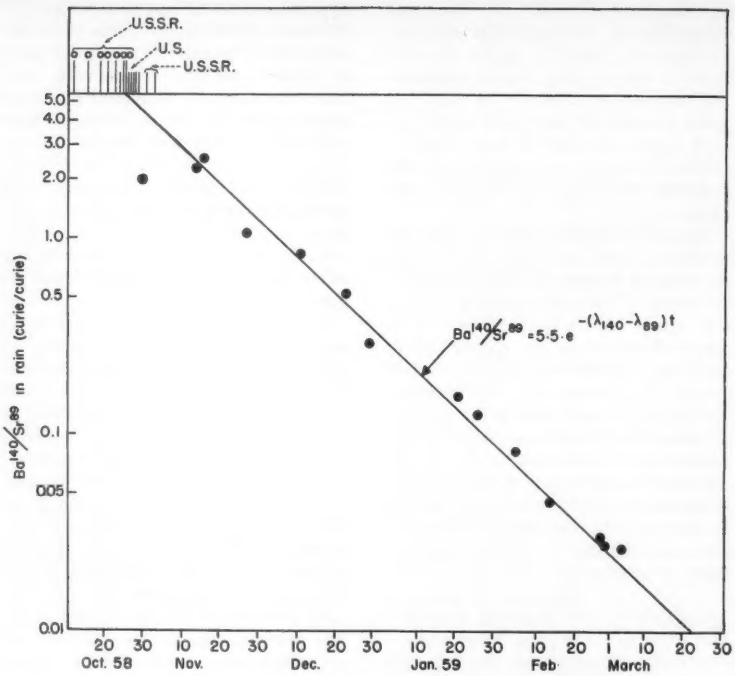


Fig. 1. Variation of the $Ba^{140}/Sr^{89}$ ratio in rain and snow.

The $Ba^{140}/Sr^{89}$ ratios in rain or snow can be expressed by the following empirical equation:

$$[Ba^{140}/Sr^{89}]_R = ke^{-(\lambda_{140}-\lambda_{89})t} \qquad (1)$$

where $[Ba^{140}/Sr^{89}]_R$ is the $Ba^{140}/Sr^{89}$ ratio in rain or snow at the time $t$ of the rainfall, $\lambda_{140}$ and $\lambda_{89}$ are the decay constants of $Ba^{140}$ and $Sr^{89}$, respectively, and $k$ is a constant.

It is interesting to note that the backward extrapolation of the straight line in Fig. 1 to 25 October 1958 gives a value for $k$ of 5.5, which is essentially the same as the $Ba^{140}/Sr^{89}$ ratio in a freshly produced fission product mixture from $U^{235}$ fission. It is known that a series of hydrogen bomb explosions occurred in the arctic during the period between 12 and 25 October 1958.

Equation 1 is a special case of the following general equation which has recently been derived by Kuroda (*2*):

$$\left(\frac{B}{A}\right)_{T,t} = \frac{\frac{k_T - k_S}{k_S} \cdot \frac{A_{T,0}}{A_{S,0}}}{[e^{(k_T-k_S)t} - 1] + \frac{k_T - k_S}{k_S} \cdot \frac{A_{T,0}}{A_{S,0}}} \times \left[\left(\frac{B}{A}\right)_{T,0} - \left(\frac{B}{A}\right)_{S,0}\right] \times e^{-(\lambda_B - \lambda_A)t} + \left(\frac{B}{A}\right)_{S,0} \times e^{-(\lambda_B - \lambda_A)t} \qquad (2)$$

where $(B/A)_{T,t}$ is the ratio of nuclides $A$ and $B$ in the troposphere at time $t$, $A_{T,0}$ and $A_{S,0}$ are the amounts of A in the troposphere and in the stratosphere at $t = 0$, $k_T$ and $k_S$ are the reciprocals of the mean storage time of the fission products in the troposphere and in the stratosphere, respectively, $(B/A)_{T,0}$ is the $B/A$ ratio in the troposphere at $t = 0$, and $(B/A)_{S,0}$ is the $B/A$ ratio in the stratosphere at $t = 0$.

Suppose that $A_{T,0}$ and $A_{S,0}$ of the nuclide $A$ were present in the tropo-

Table 1. Barium-140 and strontium-89 in rain and snow at Fayetteville, Ark.

| Date | Rainfall (in.) | $Ba^{140}$ (μμc/lit.) | $Sr^{89}$ (μμc/lit.) | $Ba^{140}/Sr^{89}$ |
|---|---|---|---|---|
| 31 Oct. 1958 | 0.17 | 2710 | 1355 | 2.00 |
| 14 Nov. 1958 | 2.00 | 569 | 246 | 2.24 |
| 16 Nov. 1958 | 1.53 | 172 | 67.9 | 2.54 |
| 27 Nov. 1958 | 0.54 (snow) | 325 | 312 | 1.04 |
| 11 Dec. 1958 | 0.10 (snow) | 114 | 138 | 0.83 |
| 23 Dec. 1958 | very slight | 203 | 392 | 0.52 |
| 30 Dec. 1958 | 0.50 | 98.2 | 352 | 0.29 |
| 21 Jan. 1959 | 0.50 (snow) | 50.3 | 320 | 0.157 |
| 26 Jan. 1959 | 0.15 | 161 | 1270 | 0.127 |
| 5 Feb. 1959 | 0.30 (snow) | 26.7 | 325 | 0.082 |
| 14 Feb. 1959 | 0.65 | 12.5 | 277 | 0.045 |
| 27 Feb. 1959 | 0.50 | 20.7 | 691 | 0.030 |
| 28 Feb. 1959 | 0.30 | 7.6 | 284 | 0.027 |
| 4 Mar. 1959 | 2.00 | 6.4 | 250 | 0.026 |

sphere and in the stratosphere, respectively, prior to a nuclear explosion ($t = 0$-), and $A^*_{T,0}$ and $A^*_{S,0}$ were added to the troposphere and to the stratosphere, respectively, by a nuclear explosion which took place at $t = 0$, and that the total quantities of $A$ in the troposphere and in the stratosphere have increased from $A_{T,0-}$ to $A_{T,0}$ and from $A_{S,0-}$ to $A_{S,0}$. Then we have the following relationships:

$$A_{T,0-} + A^*_{T,0} = A_{T,0} \quad (3)$$

$$A_{S,0-} + A^*_{S,0} = A_{S,0} \quad (4)$$

$$\left(\frac{B}{A}\right)_{T,0} = \frac{A_{T,0-} \times (B/A)_{T,0-} + A^*_{T,0} \times (y_B/y_A)}{A_{T,0-} + A^*_{T,0}} \quad (5)$$

and

$$\left(\frac{B}{A}\right)_{S,0} = \frac{A_{S,0-} \times (B/A)_{S,0-} + A^*_{S,0} \times (y_B/y_A)}{A_{S,0-} + A^*_{S,0}} \quad (6)$$

where $y_B/y_A$ is the ratio of the fission products $B$ and $A$ freshly produced by the nuclear explosion. If $A^*_{T,0} \gg A_{T,0-}$ and $A^*_{S,0} \gg A_{S,0-}$, Eqs. 5 and 6 give $(B/A)_{T,0} \cong y_B/y_A$ and $(B/A)_{S,0} \cong y_B/y_A$. By introducing these values into Eq. 2, one obtains

$$(B/A)_{T,t} = (y_B/y_A) \times e^{-(\lambda_B - \lambda_A)t} \quad (7)$$

which corresponds to the empirical relationship shown in Eq. 1.

This indicates that a very large increase of $Sr^{89}$ (and hence $Ba^{140}$) in the stratosphere must have resulted from the October 1958 hydrogen-bomb test series.

It is worthy of note that the $Sr^{89}$ concentrations in rain and snow have remained fairly constant during the past few months, despite the fact that this nuclide decays with a half-life of 54 days. A marked increase in the rate of transfer of the fission products from the stratosphere to the troposphere in early spring months, which has recently been observed by Stewart *et al.* (*3*) and also by Kuroda (*2*), seems to compensate for the expected activity decrease due to $Sr^{89}$ decay (*4*, *5*).

LOIS FRY
P. K. KURODA
*Department of Chemistry,*
*University of Arkansas, Fayetteville*

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5. This investigation was made possible by support from the U.S. Atomic Energy Commission. We are grateful to J. M. Bailey for collecting the rain samples.

6 April 1959

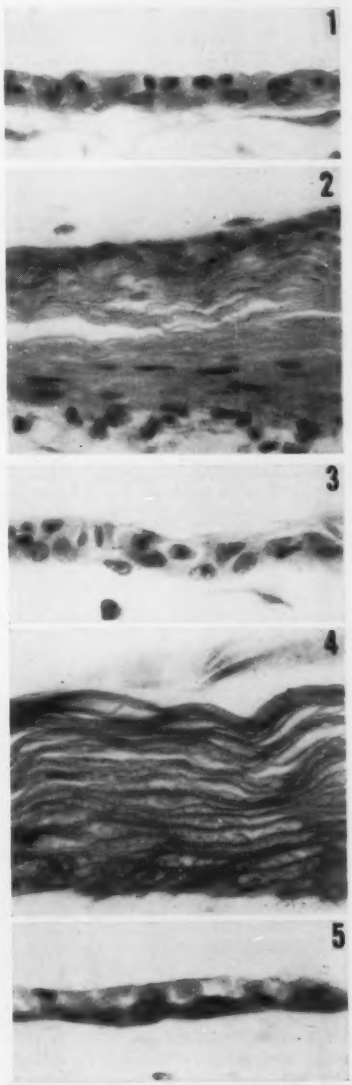
## Etiology of Keratogenic Metaplasia in the Chorioallantoic Membrane

*Abstract.* The effects of elevated $O_2$ and $CO_2$ concentrations on the occurrence of experimental keratogenic metaplasia in the chorion of the chick embryo were examined. Exposure to oxygen resulted in advanced keratinization of the chorion; carbon dioxide at elevated concentrations, in mixtures with air or oxygen, repressed the appearance of metaplastic changes, and the chorion retained its respiratory characteristics. The evidence reported here suggests that reduction of the $CO_2$ content in the gaseous environment of the chorion is causally contributory to the onset of the metaplastic events.

As reported previously (*1*), explants of the chorioallantoic membrane from 8-day chick embryos grown for 8 to 10 days in vitro as organ cultures underwent striking metaplastic changes resulting in transformation of the one-cell-thick chorion into a stratified and keratinized epithelium. It was recently found (*2*) that a similar metaplasia could be consistently produced also *in ovo* by fenestrating embryonated eggs on the 8th day of development and incubating them with the shell-window open. In such eggs there was rapid vertical proliferation of chorionic cells in the exposed area and an alteration in their protein-synthesizing activities resulting in the transformation of the attenuated chorion into a multilayered, highly cornified structure (Figs. 1, 2). The onset of metaplastic changes depended, thus, on the following major conditions: (i) detachment of the chorion from the shell membrane; (ii) exposure of the detached chorion to atmospheric air—that is, to lower carbon dioxide and higher oxygen concentrations than those in the normal environment of this respiratory epithelium. The second of these conditions is discussed in this report.

To account for the effect of exposure to outside air two possibilities were considered: (i) release from inhibition by $CO_2$, due to a decrease in its relative concentration in the chorionic environment (in this case, similarly fenestrated eggs, when exposed to elevated levels of $CO_2$, should not show metaplastic changes); (ii) activation by $O_2$ at the relatively elevated level at which it occurs in outside air (if this is the cause, exposure of chorion to pure $O_2$ should result in metaplasia, and the advent of metaplasia should not be repressible by admixture of $CO_2$).

The possibility that $CO_2$ has an inhibitory effect was tested by incubating eggs, fenestrated on the 8th day of development (a ½-square-inch window was left open), for 10 days in saturation-humidity chambers constantly gassed with a mixture of air and 5- or 8-percent $CO_2$ (*3*). Similarly prepared eggs, gassed with air, served as controls. Neither the general development nor the viability of the embryos was noticeably affected. Histological examination of the chorionic epithelium failed to reveal metaplastic changes in any of the 28 eggs




Figs. 1–5. Sections through the chorion of the chorioallantoic membrane of 18-day chick embryos fenestrated on the 8th day of development and incubated in saturation-humidity chambers. In Fig. 1 the shell-window was sealed immediately following fenestration and the embryo was incubated in air. In the other figures the shell-window was left open and the egg was incubated (Fig. 2) in air; (Fig. 3) in air plus 8-percent $CO_2$; (Fig. 4) in $O_2$; (Fig. 5) in $O_2$ plus 8-percent $CO_2$. The sections were stained with hematoxylin and Biebrich scarlet (×700).

maintained in these elevated-$CO_2$-air mixtures. The chorion retained its characteristic structure as a respiratory epithelium (Fig. 3). In contrast, all seven controls showed keratinization in the exposed area of chorion (Fig. 2). Evidently, in the presence of elevated concentrations of $CO_2$, the appearance of keratogenic changes in the appropriately prepared chorionic epithelium was completely prevented.

The effect of pure oxygen (*3*) was examined in fenestrated eggs prepared as described above and incubated till the 18th day in saturation-humidity chambers constantly gassed with oxygen. Neither the viability nor the general development of the embryos was noticeably affected. In all 35 eggs examined in this series, the exposed chorionic epithelium was found to have undergone a characteristic metaplasia into keratin-forming, multilayered epithelium (Fig. 4). In comparison with controls gassed with air, metaplasia in oxygen-gassed eggs appeared somewhat earlier in development and progressed to a more advanced stage. It was concluded that exposure to $O_2$ created conditions favorable for the initiation and rapid progression of keratogenic metaplasia. Whether $O_2$ acted as an inducing agent in setting into motion the particular metabolic and morphogenetic systems resulting in keratogenesis is, at present, an open question.

Next, the response of the chorion to $O_2$ in the presence of $CO_2$ was examined in fenestrated eggs prepared as described above and constantly gassed with a mixture of 92-percent $O_2$ and 8-percent $CO_2$. It was assumed that absence of keratinization under these conditions would support the possibility that elevated levels of $CO_2$ have an inhibitory effect on this process. Of the ten eggs examined, none showed keratinization of the chorion, and the epithelium retained its attenuated, respiratory structure (Fig. 5). Thus, the presence of one part of $CO_2$ together with 11.5 parts of $O_2$ appeared to interfere with or inhibit the appearance of metaplastic changes.

These findings suggest that the presence of $CO_2$ at concentrations higher than atmospheric concentration restricts the ability of the chorion to undergo keratogenic changes. The removal of $CO_2$ inhibition appears, therefore, to play an important—though not exclusive—role in the etiology of keratogenic metaplasia. There are various indications that $CO_2$ at increased partial pressure may be a differentiation-controlling factor (*4*). It is thus not unlikely that, in normal development, $CO_2$ promotes the respiratory differentiation of the chorion, contributing thereby to its exclusion from other metabolic and developmental courses. Removing this gaseous control mechanism creates conditions favorable for a response of this tissue to other stimuli and for the display of new developmental potentialities. Under such circumstances, $O_2$ appears to stimulate the emergence of metabolic patterns resulting in keratogenic metaplasia. Other agents may, perhaps, provoke different developmental responses (*5*).

A. Moscona
Z. I. Carneckas

*Department of Zoology,*
*University of Chicago,*
*Chicago, Illinois*

**References and Notes**

1. A. Moscona, *Proc. Soc. Exptl. Biol. Med.* **98**, 757 (1958).
2. ———*Developmental Biol.* **1**, 1 (1959).
3. The gases used in this study were purchased from the Ohio Chemical and Surgical Equipment Co., Chicago.
4. W. F. Loomis, *Science* **126**, 735 (1957).
5. This study was aided by grants from the U.S. Public Health Service (C-4272) and from the Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

27 February 1959

# Meetings

## American College of Cardiology

The American College of Cardiology, a recent affiliate of the American Association for the Advancement of Science, was organized in 1949 to fulfill the need for a wholly professional body to promote and advance clinical cardiology and angiology and to study the treatment of cardiovascular disease. The objectives of the college are, first, to provide a meeting place for the exchange of information between people doing research in this and related fields and the clinical practitioner, second, to publish a journal in clinical cardiology. The college also set up and encouraged a workshop program under which masters in particular fields of cardiological investigation invite to their laboratories or wards groups of fellows of the college for a short, intensive period of work in the special techniques available. This workshop program has been enlarged until it reaches from coast to coast, and special groups are available at practically any time of the year.

The convention of the college takes place in the spring in some center of relatively high population and includes technical and scientific exhibits. The program usually covers a variety of subjects and lasts 4 or 5 days; each segment of the program ordinarily consists of a panel discussion by men working in a particular field. There is always an attempt to have on each panel a worker in basic science, several men from the area of clinical research, and others engaged in the clinical practice of cardiology who have a particular interest or reputation in that field.

There is an interim meeting each fall; this is ordinarily held in conjunction with the faculty of a university or teaching hospital in a more lightly populated area. At the interim meetings an attempt is made to study exhaustively one or two subjects in the field of cardiology or angiology.

A special feature of each of the meetings of the college is an evening session called a "fireside conference." Tables, eight or ten in number, are set up in a large ballroom, separated from each other by a distance of 10 or 15 feet. On each there is a placard giving the subject of discussion at that table—for instance, congenital heart disease, cardiac catheterization, use of enzymes in diagnosis, diet in heart disease, treatment of angina pectoris, phonocardiography, surgical treatment of acquired heart disease, pregnancy and heart disease, and so on. At each table sit a discussion leader and the visitors who are interested in that particular subject. The discussion is completely informal, and questions and answers are fired back and forth. One can leave the group at any time and wander over to another, and there is constant circulation between the tables. Fireside conferences are ordinarily planned to last 2 hours, from 8 to 10 o'clock in the evening, but in the experience of the college, they go on until well after midnight. When the room is closed at midnight, the discussions continue in the lobby and the coffee

shop. This exchange has always been one of the most popular features of the meetings.

The current officers of the college are as follows: president, George W. Calver (Washington, D.C.); president-elect, Osler A. Abbott (Emory University, Ga.); vice presidents, Dwight E. Harken (Boston, Mass.), Ignacio Chavez (Mexico City, Mexico), Myron Prinzmetal (Beverly Hills, Calif.); secretary-treasurer and executive director, Philip Reichert (New York); assistant secretary, Henry I. Russek (Staten Island, N.Y.); assistant treasurer, Louis F. Bishop (New York). The council representative to the AAAS is George W. Calver. The office of the executive director is in the Empire State Building, 350 5th Ave., New York 1, N.Y.

PHILIP REICHERT
*American College of Cardiology, New York*

## West Central Biochemical Society

The newly formed West Central States Biochemical Society will meet in Columbia, Mo., 30–31 October. Severo Ochoa, professor of biochemistry at New York University School of Medicine, will be the guest speaker at a dinner on the opening day. Papers will be heard on 31 October, then the conference will terminate with a business meeting. For information, write to the secretary, D. F. Millikan, College of Agriculture, University of Missouri, Columbia, Mo.

## International Endocrinology Congress

The program of the first International Congress of Endocrinology, which will be held in Copenhagen 18–23 July 1960, will consist of ten symposia, a round-table discussion, and groups of shorter (10-minute) papers. Speakers at the symposia and at the round-table discussion are invited, but the short papers may be submitted. Forms for registration in the congress, along with forms for the submission of abstracts, may be obtained by writing to Dr. Svend G. Johnsen, Hormone Department, Statens Seruminstitut, Copenhagen S, Denmark. The final date for the submission of abstracts is *31 December 1959.*

The official languages of the congress are English, French, German, and Spanish. A volume containing advance abstracts of symposium contributions and the short communications (in one of the official languages and translated into Interlingua) will be distributed to members on registration at the Technical University of Denmark in Copenhagen. Titles and abstracts should not be sent to the program committee, but the pro-

gram committee will review and arrange for the presentation of such papers in appropriate congress sessions. Gregory Pincus of the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., is chairman of the Subcommittee on Program.

### Instrument Symposium and Exhibit

The ninth annual Instrument Symposium and Research Equipment Exhibit will be held 28 September–1 October, at the National Institutes of Health, Bethesda, Md. Sponsors of the exhibit are the nation's leading instrument manufacturers, who will display the newest developments in laboratory glassware and electronic, surgical, radiation, optical, gas-sampling, and other research equipment.

Sponsors of the symposium are the Washington, D.C., sections of the American Association of Clinical Chemists, American Chemical Society, Instrument Society of America, Professional Group on Medical Electronics of the Institute of Radio Engineers, Society of American Bacteriologists, and the Society for Experimental Biology and Medicine. For additional information, write James B. Davis, National Institutes of Health, Bethesda 14, Md.

### Forthcoming Events

#### July

*26–30.* International Psychoanalytical Assoc., Copenhagen, Denmark. (Miss P. King, 37 Albion St., London, W.2.)

*27–4.* International Federation of Translators, Bad Godesberg, Germany. (Dritter Internationaler FIT-Kongress, Kongress Sekretariat, Bundesverband der Dolmetscher und Übersetzer e. V. (BDÜ) Hausdorfstrasse 2, Bonn, Germany.)

*30–31.* Computers and Data Processing, 6th annual symp., Estes Park, Colo. (W. H. Eichelberger, Denver Research Inst., Univ. of Denver, Denver 10, Colo.)

#### August

*1–8.* World Congress of Esperantists, 44th, Warsaw, Poland. (Office of Intern. Conferences, Dept. of State, Washington 25.)

*4–5.* American Astronautical Soc., 2nd annual western, Los Angeles, Calif. (A. P. Mayernik, AAS, 6708 53 Rd., Maspeth 78, N.Y.)

*6–8.* Human Pituitary Hormones, colloquium (by invitation only), Buenos Aires, Argentina. (G. E. W. Wolstenholme, Ciba Foundation, 41 Portland Place, London W.2, England.)

*9–12.* American Soc. of Mechanical Engineers (Heat Transfer Div.), conf., Storrs, Conn. (D. B. MacDougall, ASME, 29 West 39 St., New York 18.)

*9–15.* Physiological Sciences, 21st intern. cong., Buenos Aires, Argentina. (C.

F. Schmidt, Univ. of Pennsylvania School of Medicine, Philadelphia 4.)

*10–13.* National Medical Assoc., Detroit, Mich. (J. T. Givens, 1108 Church St., Norfolk, Va.)

*10–13.* Society of Automotive Engineers, natl. West Coast meeting, Vancouver, B.C., Canada. (R. W. Crory, Meetings Operation Dept., SAE, 485 Lexington Ave., New York 17.)

*16–19.* Botanical Nomenclature, discussions (Intern. Bureau for Plant Taxonomy and Nomenclature), Montreal, Canada. (J. Rousseau, Natl. Museum, Ottawa, Canada.)

*16–21.* American Pharmaceutical Assoc., Cincinnati, Ohio. (R. P. Fischelis, APA, 2215 Constitution Ave., NW, Washington 7.)

*17.* Ultrasonics, natl. symp., San Francisco, Calif. (L. G. Cumming, Inst. of Radio Engineers, 1 E. 79 St., New York 21.)

*17–21.* Pacific Southwest Assoc. of Chemistry Teachers, Pacific Grove, Calif. (W. A. Craig, 416 N. Citrus Ave., Los Angeles 36, Calif.)

*17–22.* Logopedics and Phoniatrics, 11th intern. cong., London, England. (Miss P. Carter, 46 Canonbury Square, London N.1, England.)

*19–26.* Refrigeration, 10th intern. cong., Copenhagen, Denmark. (M. Kondrup, Danish Natl. Committee, Intern. Congress of Refrigeration, P.O. Box 57, Roskilde, Denmark.)

*19–29.* Botanical Cong., 9th intern., Montreal, Canada. (C. Frankton, Secretary-General, 9th Intern. Botanical Cong., Science Service Bldg., Ottawa, Ontario, Canada.)

*19–29.* International Assoc. of Wood Anatomists, Montreal, Canada. (IAWA, Laboratorium für Holzforschung E.T.H. Universitatstrasse 2, Zurich, Switzerland.)

*19–29.* Mycological Soc. of America, Montreal, Canada. (E. S. Beneke, Dept. of Botany and Plant Pathology, Michigan State Univ., E. Lansing.)

*19–29.* Phycological Soc. of America, Montreal, Canada. (W. A. Daily, Dept. of Botany, Butler Univ., Indianapolis 7, Ind.)

*20–22.* Rocky Mountain Radiological Soc., Denver, Colo. (J. H. Freed, 4200 E. Ninth Ave., Denver 20.)

*20–25.* Chemical Thermodynamics, symp., Wattens, Austria. (F. Vorländer, Deutsche Bunsen-Gesellschaft, Carl-Bosh-Haus, Varrentrappstrasse, 40–42, Frankfort a.M., Germany.)

*20–27.* Therapeutics, symp., Gardone, Italy. (R. Morf, c/o Sandoz S.A., Basel 13, Switzerland.)

*20–2.* Limnological Cong., 14th intern., Vienna and Salzburg, Austria. (Secretary, 14th Intern. Limnological Congress, Biologische Station, Lunz am See, Austria.)

*23–26.* American Farm Economic Assoc., Ithaca, N.Y. (C. D. Kearl, Dept. of Agricultural Economics, Warren Hall, Cornell Univ., Ithaca.)

*23–27.* Veterinary Medicine, 3rd Pan-American Cong., Kansas City, Mo. (B. D. Blood, Pan-American Congresses of Veterinary Medicine, P.O. Box 99, Azul, Buenos Aires Province, Argentina.)

*24–26.* American Accounting Assoc., Boulder, Colo. (C. Cox, 437 Hagerty Hall, Ohio State Univ., Columbus 10.)

*24–26.* Anti-Submarine Warfare (classified), symp., San Diego, Calif. (R. R. Dexter, Inst. of the Aeronautical Sciences, 2 E. 64 St., New York 21.)

*24–26.* Dynamics of Conducting Fluids, symp. (American Rocket Soc. and Northwestern Univ.), Evanston, Ill., (J. J. Harford, ARS, 500 Fifth Ave., New York 36.)

*24–27.* American Hospital Assoc., New York, N.Y. (E. L. Crosby, 18 E. Division St., Chicago, Ill.)

*24–28.* Australian and New Zealand Assoc. for the Advancement of Science, 34th cong., Perth, Western Australia. (J. R. A. McMillan, Science House, 157 Gloucester St., Sydney, Australia.)

*24–29.* Infrared Spectroscopy Inst., 10th annual, Nashville, Tenn. (N. Fuson, Director, Infrared Spectroscopy, Fisk Univ., Nashville 8.)

*24–29.* International Assoc. for Hydraulic Research, cong., Montreal, Canada. (IAHR, c/o Laboratoire Hydraulique, Raam 61, Delft, Netherlands.)

*24–29.* Ionization Phenomena in Gases, 4th intern. conf., Upsala, Sweden. (A. Nilsson, Secretary-General, Inst. of Physics, Upsala, Sweden.)

*24–29.* Polarography, 2nd intern. cong., Cambridge, England. (Mrs. B. Lamb, Chemistry Lab., Evershed & Vignoles, Corner of Iveagh Ave., N. Circular Rd., London N.W.10, England.)

*24–30.* Modern Systems for Detecting and Evaluating Optical Radiation (Intern. Optical Commission), symp., Stockholm, Sweden. (S. S. Ballard, Dept. of Physics, Univ. of Florida, Gainesville.)

*25–27.* Petroleum Industry Conf., AIEE, Long Beach, Calif. (N. S. Hibshman, AIEE, 33 W. 39 St., New York 18.)

*25–28.* Alaskan Science Conf., Alaskan Div., AAAS, 10th, Juneau. (N. J. Wilimovsky, Bur. of Commercial Fisheries, Box 2021, Juneau.)

*25–28.* American Dietetic Assoc., 42nd annual, Los Angeles, Calif. (Miss R. M. Yakel, ADA, 620 N. Michigan Ave., Chicago 11, Ill.)

*25–30.* American Ornithologists' Union, Regina, Saskatchewan, Canada. (H. G. Deignan, Div. of Birds, U.S. National Museum, Washington 25.)

*26–29.* International Assoc. of Milk and Food Sanitarians, Glenwood Springs, Colo. (V. T. Foley, Health Dept., Kansas City, Mo.)

*26–29.* International Union of Pure and Applied Chemistry, 20th conf., Munich, Germany. (Div. of Chemistry and Chemical Technology, Natl. Research Council, Washington 25.)

*27–29.* American Assoc., of Clinical Chemists, 11th annual, Cleveland, Ohio. (A. Hainline, Jr., AACC, Cleveland Clinic Foundation, 2020 E. 93 St., Cleveland 6.)

*27–29.* American Physical Soc., Hawaii. (K. K. Darrow, APS, Columbia Univ., New York 27.)

*28–29.* Weather Modification (with American Soc. of Civil Engineers), conf., Denver, Colo. (H. G. Houghton, AMS, Dept. of Meteorology, Massachusetts Inst. of Technology, Cambridge 39, Mass.)

*28–30.* American Folklore Soc., annual, Albany and Cooperstown, N.Y. (MacE. Leach, 110 Bennett Hall, Univ. of Pennsylvania, Philadelphia 4.)

(*See issue of 19 June for comprehensive list*)

# Letters

## Founding of Association of American Geologists

The recent article in *Science* [**129**, 1106 (1959)] entitled "Geology, geologists, and the AAAS" reminds me of the part played by the Franklin Institute in the founding of the Association of American Geologists. The organization meeting of that association was held in the hall of the Franklin Institute 2, 3, and 4 April 1840. At the request of the association an abstract of the proceedings of the meeting was prepared by its secretary, Lewis C. Beck, "for publication in the American Journal of Science, and in the Journal of the Franklin Institute." This abstract appeared in the *Journal of The Franklin Institute* in April 1840 (vol. 29, pp. 219–220) and in the *American Journal of Science* in July 1840 (vol. 39, pp. 189–191) and was also published by the association in 1843 (*Reports of the First, Second, and Third Meetings of the Association of American Geologists and Naturalists,* pages 9–11). The text is the same in all three publications, but Beck's name appears at the end of the abstract only in the *Journal of The Franklin Institute.*

The archives of the Franklin Institute contain a holographic communication, signed by Lewis C. Beck, secretary, and containing a resolution of thanks to the institute for the use of its rooms by the Association of American Geologists "during the present meeting"; it is endorsed on its back "read April 15/40." The manuscript minutes of the stated meeting of the board of managers of the Franklin Institute on 15 April 1840 record the receipt of this communication and contain its complete text. Of the 18 founders of the association, seven were members of the Franklin Institute.

JOSEPH S. HEPBURN

*Franklin Institute,*
*Philadelphia, Pennsylvania*

## Is There a Vapor Gap Around Plant Roots?

A "narrow vapor gap" around plant roots has been invoked by J. Bonner to explain the movement of water into roots without an accompanying transport of salt [*Science* **129**, 447 (1959)]. While there is a distinct need for improved theory to explain observed effects of soil salinity on plant growth, the following appear to be formidable obstacles to the vapor gap hypothesis.

The osmotic effect of salinity on plant growth in water culture is comparable to that in soil culture (*1*), and a vapor gap explanation for the osmotic gradient is, of course, out of the question in water cultures. Furthermore, the effects of salinity on plant growth are apparent at high levels of soil moisture and at low rates of water absorption from the soil. These conditions, as a matter of fact, are induced by soil salinity which reduces the rate of water uptake from soil and makes it impossible for the plant to deplete the soil moisture to values that would be obtained under nonsaline conditions. In other words, the factors that would be necessary for the development of a vapor gap, rapid water uptake and low soil-moisture content, do not usually develop in saline soils.

At low water contents, large gradients may be set up in the vicinity of the root. However, the existing data (*2*), including values estimated by Philip (*3*), indicate that, even at the dry end of the plant-growth moisture range, water movement in the liquid phase is still more important than that in the vapor phase. Under isothermal conditions, the soil-water diffusivity for vapor movement, expressed in terms of the gradient of the water content of the soil, is calculated to be of the order of $10^{-6}$ cm$^2$/sec and probably seldom exceeds $10^{-5}$

$cm^2$/sec. This is to be compared with the film-flow diffusivities of $10^{-5}$ $cm^2$/sec measured for air-dry soil and $10^{-4}$ $cm^2$/sec for soils with water contents in the wilting range. At higher water contents, the film-flow diffusivity is much greater, and is of the order of $10^{-2}$ $cm^2$/sec at the upper limit of the field moisture range. Thus, in the wilting range, film flow probably accounts for at least 90 percent of the water movement and, at higher water contents, vapor movement should be entirely negligible.

The experimental data of Gurr, Marshall, and Hutton (*4*) indicate that a temperature gradient which in their experiments averaged 1.5°C/cm is required to produce a sufficient vapor pressure gradient for the water flux density by vapor diffusion to be equal numerically to the liquid flux density in the opposite direction produced by a moderate soil-water content gradient. These experiments with a loam soil included water contents extending well into the wilting range. The vapor-gap hypothesis, therefore, would appear to require the existence of a large radial temperature gradient at the root if liquid flux is to be negligible in comparison to vapor flux. The maintenance of such a temperature gradient would require, at the root, a refrigerating system of substantial capacity.

L. Bernstein
W. R. Gardner
L. A. Richards

*Salinity Laboratory,*
*U.S. Agricultural Research Service,*
*Riverside, California*

**References**

1. H. G. Gauch and C. H. Wadleigh, *Botan. Gaz.* 105, 379 (1944).
2. W. R. Gardner and M. S. Mayhugh, *Soil Sci. Soc. Am. Proc.* 22, 197 (1958).
3. J. R. Philip, *Proc. Intern. Congr. Irrigation Drainage, 3rd Congr.* 8, 125 (1957).
4. C. G. Gurr, T. J. Marshall, J. T. Hutton, *Soil Sci.* 74, 335 (1952).

It is certainly true, as the distinguished group of Riverside investigators have pointed out, that the addition of salts to liquid nutrient solutions depresses plant growth in such solutions. The greater the ability of the test plant to accumulate the salt in question, the less is this growth-depressing effect. Thus the growth of halophytes, which readily accumulate sodium ions, is less depressed by NaCl than is the growth of crop plants which do not readily accumulate sodium ions. I grant at once, therefore, that particular ions can be found which exert osmotic effects upon plant growth, either in nutrient solution or in soil at high levels of soil moisture.

The remaining question is, then, does high soil moisture tension reduce ion uptake by the plant root? The conclusion of Philip (*1*) that development of a vapor gap around the root, under conditions of high transpiration and low soil moisture, should depress salt uptake by the root finds experimental support in the work of Danielson and Russel (*2*). These workers have shown that moisture stress generated in solution by the presence of a nonabsorbable solute (mannitol) has less effect on ion absorption than an equal moisture stress generated in soil by soil moisture tension. The results indicate that moderate-to-high soil moisture tensions interfere physically with the movement of ions from soil to root. Perhaps the physical barrier to ion movement from soil to root generated by removal of water from the soil by the root should be given a less picturesque name than "vapor gap." Nonetheless it acts like one.

James Bonner
*California Institute of Technology,*
*Pasadena, California*

**References**

1. J. R. Philip, *Proc. Intern. Congr. Irrigation Drainage, 3rd Congr.* 8, 125 (1957); *Plant Physiol.* 33, 264 (1958).
2. R. E. Danielson and M. B. Russel, *Proc. Soil Sci. Soc. Am. Proc.* 21, 3 (1957).

# New Products

■ OSCILLOSCOPE is designed primarily for high-voltage surge testing. The vertical-deflection factor is approximately 50 v/cm at an accelerating potential of 24 kv. The vertical-input system will withstand crest voltages of 3 kv of the standard 1.5- to 40-μsec surge-testing voltage. Eleven calibrated sweep rates range from 20 mμsec/cm to 50 μsec/cm. Sweep can be triggered internally or externally. Time markers are available. (Tektronix, Inc., Dept. 876)

■ MOISTURE MONITORS are designed to measure trace quantities of moisture in gases at high pressures. They will operate in air, hydrogen, nitrogen, oxygen. natural gas, hydrocarbon vapors, and helium. Pressure ratings up to 10,000 lb/in.$^2$ are available. Range is 1 to 1000 parts per million. Each monitor is equipped with a built-in pressure regulator, high- and low-pressure sample bypass, and a plug-in electrolytic cell. The instruments respond 63 percent within 90 sec to a step change in moisture content. Operation is on 105-to-125 v a-c or on self-contained battery pack. (Consolidated Electrodynamics Inc., Dept. 877)

■ MAGNETICALLY ACTUATED SWITCH is hermetically sealed in glass filled with hydrogen. Actuation can be effected by a 0.1 oz moving Alnico magnet. Contacts are rated at 125 v, 0.1 amp a-c in a model 1⅛ in. long and ¼ in. in diameter. Larger sizes are available. Operating speed is up to 60 contacts per second. Operating temperature range is −85° to +350°F. (Hamlin, Inc., Dept. 878)

■ DISPLACEMENT TRANSDUCER is a differential-transformer type in which the displacement of an armature modifies the flux paths in an *E* core. The a-c voltage output is demodulated to produce a phase-sensitive d-c output. Output is up to ± 3ma into a 2 kohm linear load with armature displacement of ± 0.03 in. The armature weighs 6 g; the remainder of the unit 30 g. Operating temperature range is −65° to +180°F. (Pneuma-Serve Ltd., Dept. 880)

BLOWERS AND CONTROL PANELS designed for installation in 19-in. electronic racks are available in two models. One, a double-outlet unit, provides high-speed delivery of 800 ft$^3$/min and low-speed delivery of 600 ft$^3$/min. The second, a single-outlet unit, provides 1200 ft$^3$/min. Filters are permanent; grilles are made of stainless steel. The motors meet MIL-E-4158 A specifications. (McLean Engineering Laboratories, Dept. 885)

■ DECIMAL SCALER designed for general radiation counting features seven decades of decimal count storage. The sensitivity of the input amplifier is 25 mv. Resolution is said to be better than 1 μsec. Discriminator and line-frequency test circuits are provided. Start and stop of the count may be controlled by present timer. (Eldorado Electronics, Dept. 886)

■ THERMOMETERS for measurement of temperature to −57°C are mercury-thallium filled glass types. The mercury-thallium amalgam is said to leave the bore clean. Seven models are available in ranges from −57° to +100°C and lengths from 9 to 18¾ in. (H. B. Instrument Co., Dept. 887)

■ OPTICAL READING HEADS for perforated tape readers are available for up to eight-bit codes. Signal-to-noise ratio is at least 8 to 1 with the paper presently being used for punched paper tape. The unit is designed to minimize the effects of changes in ambient temperature on the output signal and also to minimize the effect of aging of the photodiodes. Reading heads can be built for incorporation into customer-designed equipment. (PAR Products Corp., Dept. 890)

■ SUBCARRIER OSCILLATORS are voltage-controlled FM oscillators designed for ground-station telephone, radio, or microwave data-transmitting use. Oscillators plug into a transmitter multiplexer with conventional nine-pin connectors. Two miniature tubes are used, mounted externally to dissipate heat. Input is ±2.5 v into 500 kohm. Output is 3 v at 5 kohm from a low-pass output filter. Linearity is ±0.75 percent of bandwidth, and harmonic distortion does not exceed 0.5 percent. (Geotechnical Corp., Dept. 891)

■ FREQUENCY DIVIDER AND CLOCK accepts a stable 100 kcy/sec input and provides an essentially jitter-free tick output for comparison with a standard time signal in a time comparator. The instrument has a 3½ in. clock face, including minute and second hands. The minute hand is adjustable in 1-min steps. The second hand is continuously adjustable and has a differential tracking link to the minute hand. (Hewlett-Packard Co., Dept. 892)

■ SURFACE TEMPERATURE PROBE features a sensor of platinum wire having 500-ohm resistance at 0°C and 1/16-in. Inconel-sheathed lead that can be bent to the desired shape. Temperature limit is 760°C in a standard model; a limit of 1100°C can be provided. (Rosemount Engineering Co., Dept. 893)

JOSHUA STERN

*National Bureau of Standards, Washington, D.C.*

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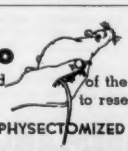

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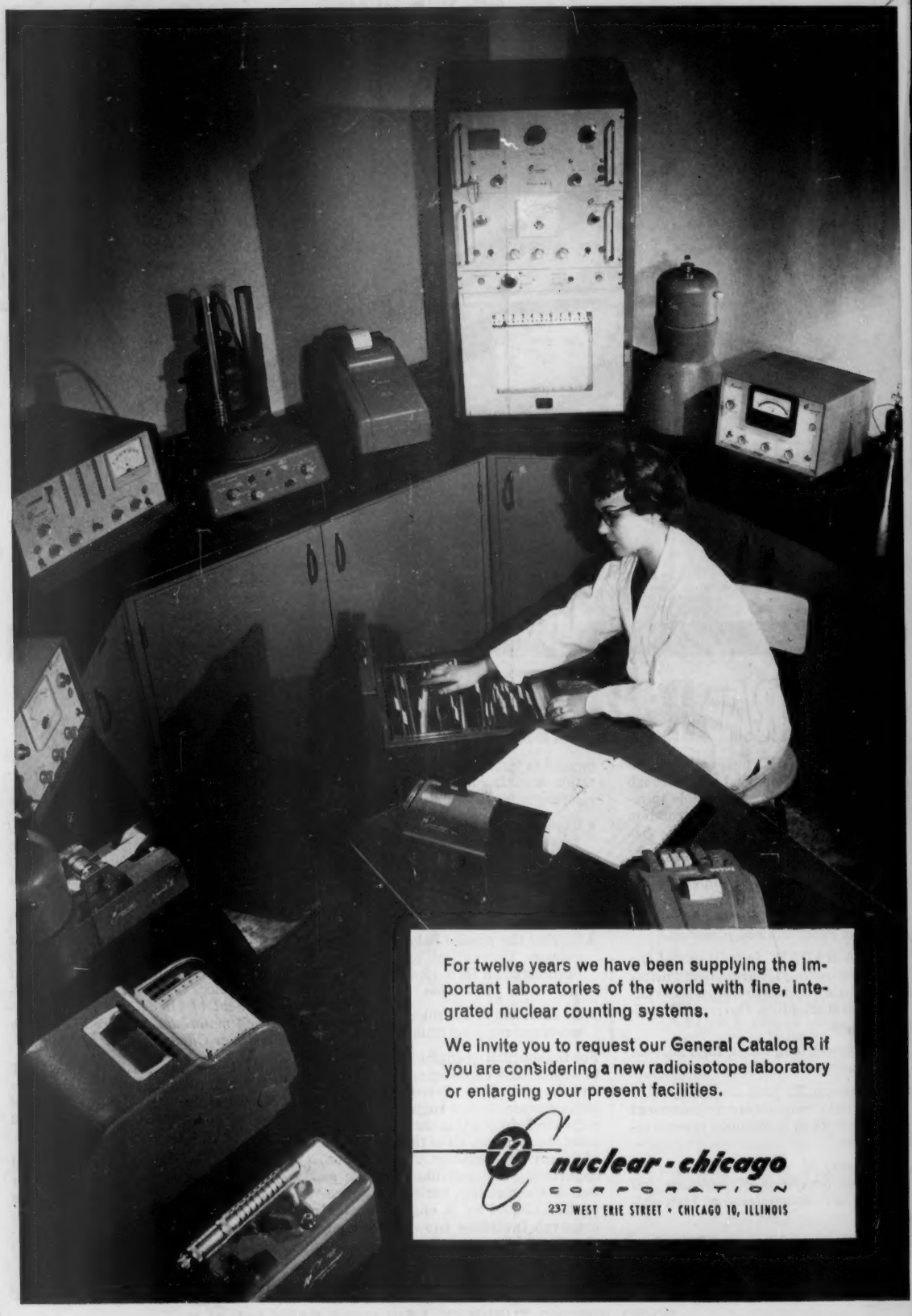

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